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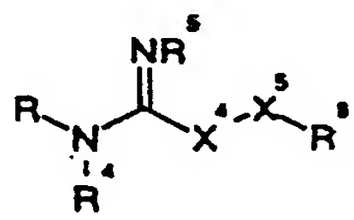
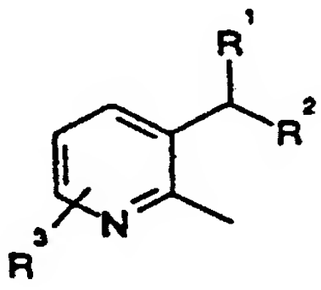
(54) Title: AMIDINE DERIVATIVES AS GASTRIC ACID SECRETION INHIBITORS

(57) Abstract

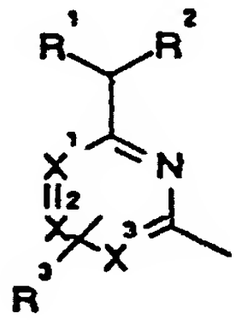
Substituted amidine derivatives of structure (I) or a salt thereof in which: R is a group of formula (i) in which R^1 is an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur; R^2 is hydrogen or C_{1-6} alkyl; R^3 is hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy; or R is a group of formula (ii) in which R^1, R^2 and R^3 are as defined in formula (i) and X^1, X^2 and X^3 are all CH groups or one of X^1, X^2 and X^3 is nitrogen and the others are CH groups; processes for their preparation, pharmaceutical compositions containing them, and their use in therapy, in particular as gastric acid secretion inhibitors, are described.



(I)



(i)



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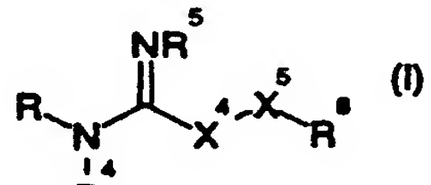
AMIDINE DERIVATIVES AS GASTRIC ACID SECRETION INHIBITORS

The present invention relates to novel substituted amidine derivatives, processes for their preparation, pharmaceutical compositions containing them, and their use in therapy, in particular as gastric acid secretion inhibitors.

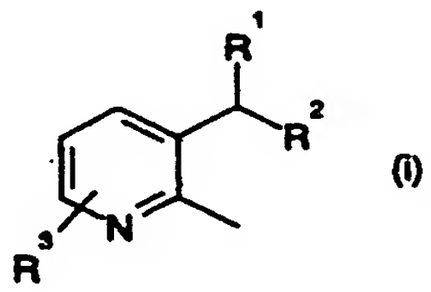
The present invention therefore provides a compound of structure (I) or a salt thereof:



(I)

in which:

R is a group of formula (i):



(i)

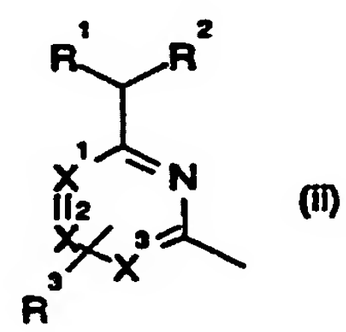
in which:

R^1 is an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 is hydrogen or C_{1-6}alkyl;

R^3 is hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

or R is a group of formula (ii):



(ii)

in which R^1, R^2 and R^3 are as defined in formula (i) above and

X^1, X^2 and X^3 are all CH groups or one of X^1, X^2 or X^3 is nitrogen and the others are CH groups;

R^4 is hydrogen or C_{1-6}alkyl;
R^5 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxy or phenyl;
X^4 is CH_2 or NR^6 where R^6 is hydrogen or C_{1-6}alkyl;
X^5 is a single bond, CH_2 or NR^7 where R^7 is hydrogen or C_{1-6}alkyl; and
R^8 is C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkylC_{3-6}cycloalkyl, C_{1-6}alkoxyC_{1-6}alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen or sulphur.

Suitably R is a group of formula (i) or (ii). When R is a group of formula (ii), X^1, X^2 and X^3 are suitably all CH groups forming a pyridine ring or one of X^1, X^2 or X^3 is nitrogen thus forming, for example when X^1 is nitrogen, a pyrimidine ring or, when X^2 is nitrogen, a pyrazine ring. Preferably, X^1, X^2 and X^3 are all CH groups.

Suitably, R^1 is an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur, for example a thienyl ring.

Suitable substituents for the phenyl and heterocyclic rings R^1 include, for example, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, halogen, cyano, amino, nitro, hydroxy, carbamoyl, carboxy, C_{1-6}alkanoyl, trifluoromethyl and C_{1-6}alkylenedioxy substituents such as methylenedioxy (-OCH_2O-). The rings may be substituted by a single substituent, or up to five substituents as may be synthetically accessible (for example, 2,3,4,5,6-penta-fluorophenyl).

Preferably, the group R^1 is thienyl, unsubstituted phenyl, or phenyl substituted by 1 or more substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, halogen, cyano, amino, hydroxy, carbamoyl, carboxy, C_{1-6}alkanoyl, trifluoromethyl or by a single substituent in association with a C_{1-4}alkylenedioxy. More preferably, R^1 is thienyl, unsubstituted phenyl, or phenyl substituted by one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, amino and nitro. Most preferably R^1 is thienyl, unsubstituted phenyl or a phenyl group substituted by a single C_{1-6}alkyl, C_{1-6}alkoxy, halogen, amino or nitro group (in particular in the 2- or 4- positions of the ring).

Suitably R^2 is hydrogen or C_{1-6}alkyl; preferably R^2 is hydrogen.

Suitably, R^3 is hydrogen, halogen, C_{1-6}alkyl or C_{1-4}alkoxy; preferably R^3 is hydrogen or C_{1-6}alkoxy.

Suitably, R^4 is hydrogen or C_{1-6}alkyl; preferably R^4 is hydrogen.

Suitably, R^5 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxy or phenyl; preferably R^5 is hydrogen.

Suitably, X^4 is CH_2 or NR^6 where R^6 is hydrogen or C_{1-6}alkyl. Preferably X^4 is NH.

Suitably X^5 is a single bond, CH_2 or NR^7 where R^7 is hydrogen or C_{1-6}alkyl, preferably X^5 is a single bond or a CH_2 group.

Suitably, R^6 is hydrogen or C_{1-6}alkyl; preferably R^6 is hydrogen.

Suitably, R^8 is C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-C_{3-6}cycloalkyl, C_{1-6}alkoxyC_{1-6}alkyl, optionally substituted phenyl or an optionally substituted 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen or sulphur. Examples of such heterocyclic rings include pyrimidine, pyrazine, and thiazole rings.

When R^8 is a phenyl ring suitable substituents include, for example, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, halogen, cyano, amino, hydroxy, carbamoyl, carboxy, C_{1-6}alkanoyl, trifluoromethyl and C_{1-4}alkylenedioxy substituents such as methylenedioxy (-OCH_2O-). The phenyl rings may be substituted by up to five substituents as may be synthetically accessible.

Preferably, R^8 is unsubstituted phenyl or phenyl substituted by a single substituent selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylsulphonyl, cyano or halogen.

Particularly preferred compounds of the invention include:

N-(6-benzyl-2-pyridyl)phenylacetamidine,
N-[6-(2-methylbenzyl)pyrid-2-yl]phenylacetamidine,
N-(2-benzyl-4-pyrimidinyl)-N'-phenylguanidine,
N-[4-(N-methylphenylamino)-2-pyrimidyl]-N'-(4-chlorophenyl)-guanidine,
N-[4-(N-methylphenylamino)-2-pyrimidyl]-N'-phenylguanidine,
N-[2-(N-methylphenylamino)-4-pyrimidyl]-N'-(4-chlorophenyl)-guanidine,
N-(4-benzyl-2-pyrimidinyl)-N'-(4-chlorophenyl)guanidine,
N-(4-benzyl-2-pyrimidinyl)-N'-phenylguanidine,
N-(6-benzylpyrazin-2-yl)-N'-phenylguanidine,
N-[6-(2-methylphenylmethyl)]pyrid-2-yl-N'-(4-chlorophenyl)-guanidine,
N-[6-(2-methylphenylmethyl)pyrid-2-yl]-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-(4-chlorophenyl)guanidine,
N-[6-(4-methylbenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-[6-(4-methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-(2-methylphenyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(2-chlorophenyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(3-methoxyphenyl)guanidine,
N-[6-(3-methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-(3-chlorophenyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(4-methoxyphenyl)guanidine,

N-(2-benzyl-3-methoxypyrid-6-yl)-N'-phenylguanidine,
N-[6-(4-fluorobenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-[6-(4-nitrobenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-[6-(4-aminophenylmethyl)pyrid-2-yl]-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-(4-cyanophenyl)guanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(4-methylthiophenyl)guanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(4-methylsulphonylphenyl)-guanidine,
N-[6-(4-methoxybenzyl)-5-methoxypyrid-2-yl]-N'-phenylguanidine,
N-[6-(4-methoxybenzyl)pyrid-2-yl]-N'-methylguanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(2-pyrimidyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-benzylguanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(2-thiazolyl)guanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(2-pyrazinyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(5-pyrimidyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(3-methoxypropyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-cyclohexylguanidine,
N-(6-benzylpyrid-2-yl)-N'-(2-methoxyethyl)guanidine,
N-[(6-benzyl)pyrid-2-yl]-N'-butylguanidine,
N-(6-benzylpyrid-2-yl)-N'-methyl-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-methyl-N"-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N',N'-dimethyl-N"-phenylguanidine,
N-[6-(3-methoxybenzyl)pyrid-2-yl]-N'-2-(2-hydroxyethyl)-N"-phenylguanidine,
N-[6-(4-methoxybenzyl)pyrid-2-yl]-N'-methyl-N"-phenyl-guanidine,
N-[6-(3-methoxybenzyl)pyrid-2-yl]-N',N"-diphenylguanidine,
N-[2-(4-methoxy)benzyl-3-methoxypyrid-6-yl]-N'-methyl-N"-phenylguanidine,
N-(3-benzylpyrid-2-yl)-N'-benzylguanidine,
N-[3-benzylpyrid-2-yl]-N'-(phenylamino)guanidine,
N-[3-(2-methylbenzyl)pyrid-2-yl]-N'-benzylguanidine,
N-[3-{4-methoxybenzyl}pyrid-2-yl]-N'-benzylguanidine,
N-[3-(4-methylbenzyl)pyrid-2-yl]-N'-(benzyl)guanidine,
N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-(4-fluorobenzyl)guanidine ,
N-[3-(thien-2-ylmethyl)pyrid-2-yl]-N'-benzylguanidine,
N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-4-cyanobenzylguanidine,
N-(3-(1-(4-methoxyphenyl)ethyl)pyrid-2-yl)-N'-benzylguanidine,
N-[3-benzylpyrid-2-yl]-N'-(2-chlorobenzyl)guanidine,
N-(3-benzylpyrid-2-yl)-N'-(4-chlorobenzyl)guanidine,
N-(3-benzylpyrid-2-yl)-N'-(4-methylbenzyl)guanidine,
N-[3-benzylpyrid-2-yl]-N'-(4-methoxybenzyl)guanidine,

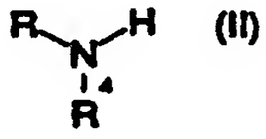
N-(3-benzylpyrid-2-yl)-N'-benzyl-N"-hydroxyguanidine,
N-[3-benzylpyrid-2-yl]-N'-benzyl-N"-methoxyguanidine,
N-(3-benzylpyrid-2-yl)-N'-phenylguanidine,
N-[3-(thien-2-ylmethyl)pyrid-2-yl]-N'-phenylguanidine,
N-[3-(4-hydroxybenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-(3-benzylpyrid-2-yl)-N'-(4-chlorophenyl)guanidine,
N-3-(4-hydroxyphenyleth-2-yl)pyrid-2-yl-N'-phenylguanidine,
N-[3-(4-methoxyphenylethen-2-yl)pyrid-2-yl]-N'-phenylguanidine, and
N-[3-benzylpyrid-2-yl]-N'-phenyl-N"-dimethylguanidine;
and pharmaceutically acceptable salts thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts including acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

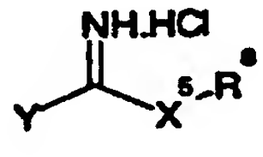
Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates. Compounds of formula (I) exist in tautomeric forms, and such tautomers also form an aspect of the invention.

The compounds of the present invention can be prepared by processes analogous to those known to those skilled in the art. In a further aspect, there is therefore provided a process for preparing compounds of structure (I) and salts thereof, which comprises

(A) for compounds in which R^5 is hydrogen; X^4 is CH_2 and X^5 is a single bond or CH_2, reaction of a compound of structure (II):


(II)

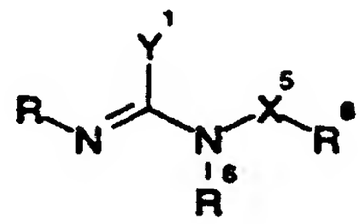
in which R and R^4 are as described for structure (I) with a compound of structure (III):


(III)

in which X^5 is a single bond or CH_2 and R^8 are as described for structure (I) and Y is a leaving group;

(B) for compounds in which X^4 is NR^6 and X^5 is a bond or NR^7, reaction of

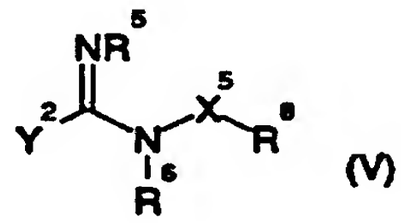
(1) a compound of structure (IV)



(IV)

in which R, R^6, R^8 are as described for structure (I), X^5 is a bond or NR^7, and Y^1 is a leaving group with an amine of structure H_2NR^5 in which R^5 is as described for structure (I); or

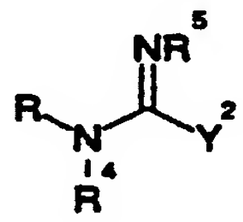
(2) reaction of a compound of structure (II) with a compound of structure (V)



(V)

in which Y^2 is a leaving group and R^5, R^6 and R^8 are as described for structure (I) and X^5 is a bond or NR^7; or

(3) reaction of a compound of structure (VI):



(VI)

in which R, R^4 and R^5 are as described for structure (I) and Y^2 is a leaving group, with a compound of structure (VII):

$$HNR^6X^5R^8 \quad \text{(VII)}$$

in which R^6 and R^8 are as described for structure (I) and X^5 is a bond or NR^7,

and optionally thereafter, forming a salt.

Suitable leaving groups Y include for example halide, or R^9O, in which R^9 is C_{1-4}alkyl. Preferably Y is R^9O.

Suitable leaving groups Y^1 include for example SH activated by mercury as described in the specific examples herein.

Suitable leaving groups Y^2 include for example OR^{10}, SR^{10}, halogen or sulphonic acid, in which R^{10} is C_{1-4}alkyl or optionally substituted aryl groups; preferred groups Y^2 include SR^{10} groups, in particular SCH_3.

The reaction between compounds of structure (II) and compounds of structure (III) can be carried out in a suitable solvent at a temperature of between 0°C and the reflux temperature of the solvent used, for as long as it takes for complete reaction to occur. Suitable solvents include, for example, C_{1-4}alkanols such as ethanol or methanol. Preferably, the reaction can be carried out in ethanol as a solvent, at ambient temperature.

The reaction between compounds of structure (IV) with an amine H_2NR^5 can be carried out in the presence of a suitable solvent such as a C_{1-4}alkanol, in particular methanol, at ambient temperature or elevated temperature, until reaction is complete.

The reaction between compounds of structure (II) and (V) can be carried out in the presence of a suitable solvent such as a C_{1-4}alkanol such as methanol or ethanol.

The reaction between a compound of structure (VI) and an amine of structure (VII) can be carried out in the presence of a suitable solvent such as a C_{1-4}alkanol such as methanol or ethanol.

The intermediate compounds of structures (II), (III) and (IV) can be prepared from commercially available starting materials, using standard techniques practised in the art of organic chemistry. For example, compounds of structure (II) can be prepared by reaction of the appropriate halo derivative with an amine R^4NH_2, in which R^4 is as described for structure (I), in a suitable solvent. Compounds of structure (III), for example, in which R^9 is ethyl, can be prepared by reaction of the appropriate cyano derivative R^8CH_2CN,in which R^8 is as described for structure (I), with dry hydrogen chloride gas in ethanol as a reaction solvent.

Compounds of structure (IV), for example, in which R^6 is hydrogen, can be prepared by reaction of an appropriate amino derivative with an isothiocyanate R^8NCS in which R^8 is as described for structure (I) in a suitable solvent.

The compounds of structure (I) and their pharmaceutically acceptable salts exert an anti-secretory effect by inhibition of the gastrointestinal H^+K^+ATPase enzyme (Fellenius, E., Berglindh, T., Sachs, G., Olke, L., Elander, B., Sjostrand, S.E., and Wallmark, B., 1981, Nature, 290, 159-61).

In a further aspect therefore the present invention provides compounds of structure (I) and pharmaceutically acceptable salts thereof for use in therapy. The compounds of structure (I) and their pharmaceutically acceptable salts inhibit exogenously and endogenously stimulated gastric acid secretion and are useful in the treatment of gastrointestinal diseases in mammals, in particular humans.

Such diseases include, for example, gastric and duodenal ulcers, aspiration pneumonitis and Zollinger-Ellison Syndrome.

Further, the compounds of structure (I) can be used in the treatment of other disorders where an anti-secretory effect is desirable for example in patients with gastritis, NSAID induced gastritis, acute upper intestinal bleeding, in patients with a history of chronic and excessive alcohol consumption, and in patients with gastro oesophageal reflux disease (GERD).

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains suitably from 1 to 1000 mg, preferably from 1 to 500 mg (and for parenteral administration contains preferably from

0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The present invention also provides a method of inhibiting gastric acid secretion which comprises administering to a mammal in need thereof an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof; and a method of treatment of diseases of the stomach or intestine based on increased acid secretion which comprises administering to a mammal in need thereof an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of gastrointestinal disorders, in particular the treatment of diseases of the stomach or intestine caused by increased acid secretion.

Compounds of the invention will normally be administered to a subject for the treatment of gastrointestinal diseases and other conditions caused or exacerbated by gastric acidity. The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

In addition, the compounds of the present invention can be co-administered with further active ingredients, such as antacids (for example magnesium carbonate or hydroxide and aluminium hydroxide), non-steroidal anti-flammatory drugs (for example indomethacin, aspirin or naproxen), steroids, or nitrite scavengers (for example ascorbic acid or aminosulphonic acid), or other drugs used for treating gastric ulcers (for example histamine H_2-antagonists such as cimetidine) or agents having activity against Helicobacter pylori organisms, for example antibiotics such as amoxicillin.

The following examples illustrate the invention. Temperatures are recorded in degrees centigrade.

Example 1

N-(6-Benzyl-2-pyridyl)phenylacetamidine maleate

(a) 2-Bromo-6-benzylpyridine

Powdered zinc (24.51 g, 0.375 mol) and chlorotrimethylsilane (3.25 g, 0.03 mol) in dry tetrahydrofuran (500 ml) were stirred under nitrogen for 15 min. Benzyl bromide (51.31 g, 0.3 mol was then added dropwise, keeping the temperature below 35° (cold water bath). After a further 1 hr, the excess zinc was allowed to settle, and the solution decanted onto a solution of 2,6-dibromopyridine (59.23 g, 0.25 mol) in dry tetrahydrofuran (200 ml), washing the solid with tetrahydrofuran (100 ml). Tetrakis-(triphenylphosphine)palladium(0) (2.89 g, 0.0025 mol) was then added, and the mixture stirred at room temperature under nitrogen for 16 hr. Saturated aqueous ammonium chloride (500 ml) was then added, and the mixture extracted three times with ether. The combined extracts were dried ($MgSO_4$) and evaporated to an oily solid, which was purified by flash chromatography (dichloromethane/pet. ether) to give the title compound as a clear oil. Yield 39.37 g (63%).

(b) 2-Hydrazino-6-benzylpyridine

A mixture of 2-bromo-6-benzylpyridine (12.0 g, 0.048 mol), ethanol (50 ml) and hydrazine hydrate (50 ml) was heated at 160 °C in a pressure vessel for 2.5 hours. The solvent was removed *in vacuo* and to the residue was added aqueous sodium hydroxide solution. The resulting solid was filtered off and washed with water. Yield 8.47 g (88%), m.p. 80-82 °C.

(c) 2-Amino-6-benzylpyridine

Method 1. A mixture of 2-bromo-6-benzylpyridine (8.54 g, 0.002 mol) and 25% ammonium hydroxide solution (50 ml) was heated at 190 °C in a pressure vessel for 16 hours. The mixture was basified to pH 14 with concentrated aqueous sodium hydroxide solution and extracted twice with diethyl ether. The organic extracts were combined, dried and the solvent removed *in vacuo*, and the residue was purified by flash chromatography (5% methanol in dichloromethane) to give the product as a brown oil. Yield 1.45 g (23%).

Method 2. A mixture of 2-hydrazino-6-benzylpyridine (8.47g, 0.043 mol), Raney nickel (1 spoonful) and ethanol (120 ml) was hydrogenated at 50 psi and 50 °C for 3 hours, then the catalyst was removed by filtration. Evaporation of the solvent and trituration with petroleum ether gave a white crystalline product. Yield 5.94 g (96%), m.p. 54-56 °C.

(d) N-(6-Benzyl-2-pyridyl)phenylacetamidine maleate

A solution of 2-amino-6-benzylpyridine (1.43 g, 0.0078 mol) and ethyl phenylacetimidate hydrochloride (2.33 g, 0.0116 mol) in ethanol (50 ml) was left to stand for 4 days at room

temperature. The solvent was evaporated and the residue purified by flash chromatography (2-6% methanol in dichloromethane) to give an oil. This was treated with water, made strongly basic with concentrated aqueous sodium hydroxide, and extracted three times with dichloromethane. The combined extracts were dried (K_2CO_3) and evaporated to an oil (0.85 g) which was dissolved in a solution of maleic acid (0.33 g) in ethanol and treated with ether to give a white crystalline solid. Recrystallisation from acetonitrile afforded the product as the monomaleate salt. Yield 0.53 g (16%), m.p. 138-140°C.

$C_{20}H_{19}N_3 .C_4H_4O_4$

Found C 68.94, H 5.51, N 10.03 Expected C 69.05, H 5.55, N 10.07

Example 2

N-[6-(2-Methylbenzyl)pyrid-2-yl]phenylacetamidine maleate

(a) 2-Bromo-6-(2-methylbenzyl)pyridine hydrobromide

Powdered zinc (7.36 g, 0.113 mol) and chlorotrimethylsilane (0.92 g, 0.00844 mol) in dry tetrahydrofuran (160 ml) were stirred under nitrogen for 45 min. a-Bromo-*o*-xylene (11.31 ml, 0.0844 mol) was then added dropwise, keeping the temperature below 35 °C (cold water bath). After a further 1 hr, the excess zinc was allowed to settle, and the solution decanted onto 2,6-dibromopyridine (20 g, 0.0844 mol), washing the solid with dry tetrahydrofuran. Tetrakis(triphenylphosphine)palladium(0) (0.98 g, 0.00084 mol) was then added, and the mixture heated under nitrogen with stirring at 55 °C for 20 hours. Saturated aqueous ammonium chloride (200 ml) was then added, and the mixture extracted three times with ether. The combined extracts were dried (K_2CO_3) and evaporated to an oily solid, which was dissolved in a solution of 45% w/v HBr in acetic acid (30 ml). Treatment with ether afforded a crystalline solid which was filtered off and recrystallised from chloroform/ether. Yield 14.44 g (50%), m.p. 184-186 °C.

(b) 2-Amino-6-(2-methylbenzyl)pyridine

2-Bromo-6-(2-methylbenzyl)pyridine hydrobromide (7.0 g, 0.0204 mol) and 25% aqeous ammonia (50 ml) were heated with stirring at 200 °C in a pressure vessel for 20 hr. The mixture was then made strongly basic with concentrated aqueous sodium hydroxide and extracted twice with chloroform. The combined extracts were dried (K_2CO_3) and evaporated to an oil which was purified by flash chromatography (methanol/dichloromethane). The product crystallised under pet. ether (b.p. 60-80). Yield 1.8 g (45%), m.p. 54-57 °C.

(c) N-[6-(2-Methylbenzyl)pyrid-2-yl]phenylacetamidine maleate

2-Amino-6-(2-methylbenzyl)pyridine (1.12 g, 0.0057 mol) and ethyl phenylacetimidate

hydrochloride (1.70 g , 0.0085 mol) were stirred in ethanol (50 ml) for 4 days. The solvent was evaporated, and the residue purified by flash chromatography (2-4% methanol in dichloromethane). The resulting product was treated with water and basified with sodium hydroxide solution (conc) to pH 14, then extracted with dichloromethane twice and the combined extracts dried (K_2CO_3) and evaporated to an oil (0.5 g). Treatment with maleic acid in a small amount of ethanol, followed by addition of ether afforded the product as the monomaleate salt. Yield 0.35 g, m.p. 149 °C

$C_{21}H_{21}N_3 .C_4H_4O_4$

Found C 69.85, H 5.95, N 9.98 Expected C 69.59, H 5.84, N 9.74

Example 3

N-(2-Benzyl-4-pyrimidinyl)-N'-phenylguanidine

(a) 2-Benzyl-4-pyrimidone

A solution of ethyl sodioformyl acetate (23.56 g, 0.17 mol) in water was added to a solution of phenylacetamidine hydrochloride (10.24 g, 0.06 mol) in aqueous sodium hydroxide (3.59 g of NaOH in 35 ml of water) and the mixture left to stand for 4 days. After briefly heating on a water bath, the solution was acidified with glacial acetic acid, and the resulting solid filtered off, washed, and recrystallised from ether/pet. ether. Yield 9.2 g (96%).

(b) 2-Benzyl-4-chloropyrimidine

2-Benzyl-4-pyrimidone (1.65 g, 0.01 mol) was suspended in phosphoryl chloride (20 ml, excess) and the mixture refluxed for 30 min. Excess phosphoryl chloride was evaporated off, and the residue treated with ice, made strongly basic with concentrated aqueous sodium hydroxide, and extracted three times with chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to a brown oil. Yield 1.15 g (55%).

(c) 2-Benzyl-4-aminopyrimidine

A solution of 2-benzyl-4-chloropyrimidine (1.15 g, 0.0056 mol) in ammonia-saturated methanol (50 ml) was heated at 125 °C for 2 hours in a pressure vessel. The solvent was evaporated, and the residue treated with water, made strongly basic with concentrated aqueous sodium hydroxide, and extracted three times with chloroform. The combined extracts were dried (K_2CO_3) and evaporated to a solid, which was triturated with pet. ether. Yield 0.71 g, m.p.140-143 °C.

(d) N-(2-benzyl-4-pyrimidinyl)-N'-phenylthiourea

To a suspension of sodium hydride (60% dispersion in oil, 0.34 g, 0.0084 mol) in toluene (20 ml) at 100 °C was added in portions 2-benzyl-4-aminopyrimidine (1.3 g, 0.007 mol). The mixture was refluxed for 30 min, then phenyl isothiocyanate (1.14 g, 0.0084 mol) was

added. Reflux was continued for a further 2 hours, then the reaction allowed to cool. Treatment with water and chloroform afforded a white solid. Yield 1.07 g (48%), m.p. 191-193°C.

(e) N-(2-Benzyl-4-pyrimidinyl)-N'-phenylguanidine

To a stirring suspension of N-(2-benzyl-4-pyrimidinyl)-N'-phenylthiourea (1.01 g, 0.00315 mol) in ammonia-saturated methanol (25 ml) was added yellow mercuric oxide (0.82 g, 0.00378 mol). Stirring was continued for 16 hr, then the solvent evaporated and the black residue boiled with chloroform and filtered. The filtrate was evaporated to a white solid, which was recrystallised from acetonitrile. Yield 0.68 g (71%), m.p. 175-177°C.

$C_{18}H_{17}N_5$ Found C 71.13, H 5.70, N 23.03 Expected C 71.27, H 5.65, N 23.09

Example 4

N-[4-(N-Methylphenylamino)-2-pyrimidyl]-N'-(4-chlorophenyl)guanidine

(a) 2-Amino-4-chloropyrimidine and 4-amino-2-chloropyrimidine

2,4-Dichloropyrimidine (10 g, 67 mmol) was dissolved in ethanolic ammonia (35 ml) and stirred at room temperature for 48 hours, then the resulting white precipitate was filtered off and washed with water. This proved to be a mixture of isomers (7.64 g), which was used without purification.

(b) 2-Amino-4-(N-methylphenylamino)pyrimidine and 4-amino-2-(N-methylphenylamino)pyrimidine

The mixture of aminochloropyrimidines from the previous step (7.0 g) was heated with N-methylaniline (11.7 ml, 108 mmol) at 150 °C for 3 hours, then poured into aqueous sodium bicarbonate and extracted with chloroform. Drying, evaporation of the chloroform, and chromatography (silica, 3% methanol in dichloromethane) gave 4-amino-2-(N-methylphenylamino)pyrimidine (1.4 g, m.p. 120-122 °C) and 2-amino-4-(N-methylphenylamino)pyrimidine (0.8 g, m.p. 115-118 °C).

(c) N-[4-(N-Methylphenylamino)-2-pyrimidyl]-N'-(4-chlorophenyl)thiourea

A mixture of 2-amino-4-(N-methylphenylamino)pyrimidine (2.29 g, 11.4 mmol) and 4-chlorophenyl isothiocyanate (2.55 g, 12.6 mmol) in ethanol (50 ml) was stirred at reflux for 5 hours, then cooled. The crystalline product was filtered off and washed with ether. Yield 3.6 g (86%), m.p. 202-204 °C.

(d) N-[4-(N-Methylphenylamino)-2-pyrimidyl]-N'-(4-chlorophenyl)guanidine

A mixture of N-[4-(N-methylphenylamino)-2-pyrimidyl]-N'-(4-chlorophenyl)thiourea (2.2 g, 6.0 mmol), mercuric oxide (1.54 g, 7.1 mmol) and methanolic ammonia (50 ml) was stirred at room temperature for 48 hours.. The solvent was removed *in vacuo* and the resulting black solid was boiled with chloroform and filtered hot. The filtrate was

evaporated and the product purified by chromatography (silica, 0-10% methanol in chloroform). Yield 0.62 g (30%), m.p. 115-120 °C.

$C_{18}H_{17}ClN_6 .0.25HCl$

Found C 59.37, H 4.87, N 23.02, Cl 12.02 Requires C 59.73, H 4.80, N 23.22, Cl 12.24

Example 5

N-[4-(N-Methylphenylamino)-2-pyrimidyl]-N'-phenylguanidine

(a) N-[4-(N-Methylphenylamino)-2-pyrimidyl]-N'-phenylthiourea

A mixture of 2-amino-4-(N-methylphenylamino)pyrimidine (1.0 g, 5 mmol) and phenyl isothiocyanate (0.8 g, 6 mmol) in toluene (20 ml) was stirred at reflux for 18 hours, then cooled and diluted with ether. The crystalline product was filtered off and washed with ether. Yield 1.2 g (72%), m.p. 189-192 °C.

(b) N-[4-(N-Methylphenylamino)-2-pyrimidyl]-N'-phenylguanidine

A mixture of N-[4-(N-methylphenylamino)-2-pyrimidyl]-N'-phenylthiourea (1.0 g, 3.0 mmol), mercuric oxide (0.77 g, 3.4 mmol) and methanolic ammonia (50 ml) was stirred at room temperature for 48 hours.. The solvent was removed *in vacuo* and the resulting black solid was boiled with chloroform and filtered hot. The filtrate was evaporated and the product purified by chromatography (silica, 0-10% methanol in chloroform). Yield 0.30 g (32%), m.p. 174-177 °C.

$C_{18}H_{18}N_6 .0.1H_2O$

Found C 67.33, H 5.81, N 25.93 Requires C 67.54, H 5.80, N 26.26

Example 6

N-[2-(N-Methylphenylamino)-4-pyrimidyl]-N'-(4-chlorophenyl)guanidine hydrochloride

(a) N-[2-(N-Methylphenylamino)-4-pyrimidyl]-N'-phenylthiourea

A mixture of 4-amino-2-(N-methylphenylamino)pyrimidine (1.1 g, 5.5 mmol) and 4-chlorophenyl isothiocyanate (1.12 g, 6.6 mmol) in toluene (25 ml) was stirred at reflux for 3 hours, then cooled and diluted with ether. The crystalline product was filtered off and washed with ether. Yield 0.62 g (31%)

(b) N-[2-(N-Methylphenylamino)-4-pyrimidyl]-N'-phenylguanidine

A mixture of N-[2-(N-methylphenylamino)-4-pyrimidyl]-N'-phenylthiourea (0.62 g, 1.85 mmol), mercuric oxide (0.47 g, 2.22 mmol) and methanolic ammonia (50 ml) was stirred at room temperature for 16 hours.. The solvent was removed *in vacuo* and the resulting black solid was boiled with chloroform and filtered hot. The filtrate was evaporated and

the product purified by chromatography (silica, 0-10% methanol in chloroform) and trituration with ether. Yield 0.07 g (11%), m.p. 152-157 °C.

$C_{18}H_{17}ClN_6$ .HCl

Found C 55.34, H 4.44, N 21.69 Requires C 55.53, H 4.66, N 21.58

Example 7

N-(4-Benzyl-2-pyrimidinyl)-N'-(4-chlorophenyl)guanidine

(a) 2-Chloro-4-benzylpyrimidine

Powdered zinc (11.67 g, 0.179 mol) and chlorotrimethylsilane (1.68 ml, 0.0134 mol) in dry tetrahydrofuran (250 ml) were stirred under nitrogen for 40 min. Benzyl bromide (22.96 g, 0.134 mol) was then added dropwise, keeping the temperature below 40 °C (cold water bath). After a further 2 hours the excess zinc was allowed to settle, and the solution decanted onto 2,4-dichloropyrimidine (20 g, 0.134 mol), washing the solid with tetrahydrofuran. Tetrakis(triphenylphosphine)palladium(0) (1.55 g, 0.00134 mol) was then added, and the mixture stirred at room temperature under nitrogen for 40 hours. Saturated aqueous ammonium chloride was then added, and the mixture extracted three times with ether. The combined extracts were dried ($MgSO_4$) and evaporated to a yellow oil (37 g), which was purified by flash chromatography (dichloromethane-pet. ether) to give the title compound as a clear oil. Yield 14.02 g (51%).

(b) 2-Amino-4-benzylpyrimidine

A solution of 2-chloro-4-benzylpyrimidine (7 g, 0.0342 mol) in ammonia-saturated methanol (60 ml) was heated at 150 °C for 3 hours in a pressure vessel. The solvent was evaporated, and the residue treated with water, and made strongly basic with concentrated aqueous sodium hydroxide. The resulting solid was filtered off, washed with water and recrystallised from ethanol to give the title compound. Yield 4.19 g (66%), m.p. 147-149 °C.

(c) N-(4-Benzyl-2-pyrimidinyl)-N'-(4-chlorophenyl)thiourea

A stirring mixture of 2-amino-4-benzylpyrimidine (1 g, 0.0054 mol) and 4-chlorophenylisothiocyanate (1.1 g, 0.00648 mol) in toluene (5 ml) was heated under reflux with stirring for 3 hours. After allowing to cool, the solution was treated with ether, and the resulting solid filtered, washed and dried. Yield 1.12 g (58%), m.p. 204-206 °C.

(d) N-(4-Benzyl-2-pyrimidinyl)-N'-(4-chlorophenyl)guanidine

To a stirring suspension of N-(4-benzyl-2-pyrimidinyl)-N'-(4-chlorophenyl)thiourea (1.08 g, 0.00304 mol) in ammonia-saturated methanol (30 ml) was added yellow mercuric oxide (0.79 g, 0.00365 mol). Stirring was continued for 30 hr, then the solvent evaporated and the black residue boiled with chloroform and filtered. The filtrate was evaporated and

the product purified by flash chromatography (methanolic ammonia in dichloromethane). The resulting solid was recrystallised from ethanol to give the title compound.
Yield 0.67 g (65%), m.p 190-191 °C.
$C_{18}H_{16}N_5$. Found C 63.98, H 4.87, N 20.66 Expected C 64.00, H 4.77, N 20.73

Example 8
N-(4-Benzyl-2-pyrimidinyl)-N'-phenylguanidine

(a) N-(4-Benzyl-2-pyrimidinyl)-N'-phenylthiourea
A stirring mixture of 2-amino-4-benzylpyrimidine (1 g, 0.0054 mol) and phenyl isothiocyanate (0.88 g, 0.0065 mol) in toluene (5 ml) was heated under reflux with stirring for 5 hr. After allowing to cool, the solution was treated with ether, and the resulting solid filtered off, washed and dried. Yield 0.9 g (52%), m.p. 174-176 °C.

(b) N-(4-Benzyl-2-pyrimidinyl)-N'-phenylguanidine
To a stirring suspension of N-(4-benzyl-2-pyrimidinyl)-N'-phenylthiourea (0.88 g, 0.00275 mol) in ammonia-saturated methanol (25 ml) was added yellow mercuric oxide (0.71 g, 0.0033 mol). Stirring was continued for 48 hr, then the solvent evaporated and the black residue boiled with chloroform and filtered. The filtrate was evaporated to an oil, which crystallised from ethanol. Yield 0.36 g (43%), m.p. 152-153 °C.
$C_{18}H_{17}N_5$. Found C 71.10, H 5.59, N 22.74 Expected C 71.27, H 5.65, N 23.09

Example 9
N-(6-Benzylpyrazin-2-yl)-N'-phenylguanidine

(a) 2-Chloro-6-benzylpyrazine
Powdered zinc (7.42 g, 0.1134 mol) and chlorotrimethylsilane (0.95 g, 0.0087 mol) in dry tetrahydrofuran (160 ml) were stirred under nitrogen for 15 min. Benzyl bromide (14.92 g, 0.087 mol) was then added dropwise, keeping the temperature below 40 °C (cold water bath). After a further 3 hr, the excess zinc was allowed to settle, and the solution decanted onto 2,6-dichloropyrazine (13 g, 0.087mol), washing the solid with tetrahydrofuran. Tetrakis(triphenylphosphine)palladium(0) (1.01 g, 0.00087 mol) was then added, and the mixture stirred at room temperature under nitrogen for 5 days. Saturated aqueous ammonium chloride was then added, and the mixture extracted three times with ether. The combined extracts were dried ($MgSO_4$) and evaporated to a dark liquid, which was purified by flash chromatography (dichloromethane-pet. ether) to give the title compound as a clear oil. Yield 3.75 g (21%).

(b) 2-Amino-6-benzylpyrazine

A solution of 2-chloro 6-benzylpyrazine (3.7g, 0.018 mol) in ammonia-saturated methanol (50 ml) was heated at 180 °C for 16 hr. in a pressure vessel. The solvent was evaporated, and the residue treated with water, and made strongly basic with concentrated aqueous sodium hydroxide. The mixture was extracted three times with ether, and the combined extracts dried (K_2CO_3) and evaporated to an oil, which crystallised from ether/pet. ether. Yield 1.92 g (57%), m.p. 166-167 °C

(c) N-(6-Benzylpyrazin-2-yl)-N'-phenylthiourea

A mixture of 2-amino-6-benzylpyrazine (1.91 g, 0.0103 mol) and phenyl isothiocyanate (1.67 g, 0.0124 mol) in toluene (10 ml) was heated under reflux with stirring for 3 hr. After allowing to cool, the solution was treated with ether, and the resulting solid filtered off, washed and dried. Yield 1.36 g (41%), m.p 192-194 °C.

(d) N-(6-Benzylpyrazin-2-yl)-N'-phenylguanidine

To a stirring suspension of N-(6-benzylpyrazin-2-yl)-N'-phenylthiourea (1.3 g, 0.0041 mol) in ammonia-saturated methanol (40 ml) was added yellow mercuric oxide (1.05 g, 0.0049 mol). Stirring was continued for 4 days, then the solvent evaporated and the black residue boiled with chloroform and filtered. The filtrate was evaporated to an oil, which was dissolved in ethanol, and refiltered. Removal of the ethanol *in vacuo* followed by treatment with acetonitrile gave the product as a white crystalline solid. Yield 1.06 g (86%), m.p. 165-167 °C.

$C_{18}H_{17}N_5$ Found C 70.89, H 5.67, N 22.93 Expected C 71.27, H 5.65, N 23.09

Example 10

N-[6-(2-Methylphenylmethyl)]pyrid-2-yl-N'-(4-chlorophenyl)guanidine

(a) N-[6-(2-Methylphenylmethyl)]pyrid-2-yl-N'-(4-chlorophenyl)thiourea

A mixture of 2-amino-6-(2-methylphenylmethyl)pyridine (0.9 g, 0.00454 mol) and 4-chlorophenyl isothiocyanate (0.92 g, 0.00545 mol) in toluene (4 ml) was heated under reflux with stirring for 2.5 hr. After allowing to cool, the solution was treated with ether, and the resulting solid filtered off, washed and dried. Yield 1.46 g (87%), m.p. 218-221 °C.

(b) N-[6-(2-Methylphenylmethyl)]pyrid-2-yl-N'-(4-chlorophenyl)guanidine

To a suspension of N-[6-(2-methylphenylmethyl)]pyrid-2-yl-N'-(4-chlorophenyl)thiourea (1.42 g, 0.0039 mol) in ammonia-saturated methanol (35 ml) was added yellow mercuric oxide (1.0 g, 0.0046 mol). Stirring was continued for 16 hr, then the solvent evaporated and the black residue boiled with chloroform and filtered. The filtrate was evaporated to a solid, which was purified by flash chromatography (methanolic ammonia in chloroform). The crystalline product was triturated with etherd. Yield 0.42 g (30%), m.p. 209-211 °C.

$C_{20}H_{19}ClN_4$ .0.15$CHCl_3$
Found C 65.76, H 5.29, N 15.35 Expected C 65.66, H 5.24, N 15.20

Example 11
N-[6-(2-Methylphenylmethyl)pyrid-2-yl]-N'-phenylguanidine

(a) N-[6-(2-Methylphenylmethyl)pyrid-2-yl]-N'-phenylthiourea
A mixture of 2-amino-6-(2-methylphenylmethyl)pyridine (0.87 g, 0.0044 mol) and phenyl isothiocyanate (0.71 g, 0.0053 mol) in toluene (4 ml) was heated under reflux with stirring for 3.5 hr. After allowing to cool, the solution was treated with ether, and the resulting solid filtered off, washed and dried. Yield 1.1 g (75%), m.p. 184-186 °C.

(b) N-[6-(2-Methylphenylmethyl)pyrid-2-yl]-N'-phenylguanidine
To a suspension of N-[6-(2-methylphenylmethyl)pyrid-2-yl]-N'-phenylthiourea (1 g, 0.003 mol) in ammonia-saturated methanol (30 ml) was added yellow mercuric oxide (0.78 g, 0.0036 mol). Stirring was continued for 48 hr, then the solvent evaporated and the black residue boiled with chloroform and filtered. The filtrate was evaporated to half volume, when a solid crystallised out. This was filtered off, and purified by flash chromatography (ammoniacal methanol-chloroform). The product was recrystallised from methanol. Yield 0.46 g (48%), m.p 176-178 °C.
$C_{20}H_{20}N_4$. Found C 75.94, H 6.33, N 17.78 Expected C 75.92, H 6.37, N 17.71

Example 12
N-(6-Benzylpyrid-2-yl)-N'-phenylguanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-phenylthiourea
A mixture of 2-amino-6-benzylpyridine (1.43 g, 0.0084 mol) and phenyl isothiocyanate (1.36 g, 0.01 mol) in toluene (7 ml) was heated under reflux with stirring for 3.5 hr. After allowing to cool, the solution was treated with ether, and the resulting solid filtered off, washed and dried. Yield 1.2 g (45%), m.p. 163-165 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-phenylguanidine
To a suspension of N-(6-Benzylpyrid-2-yl)-N'-phenylthiourea (1.2 g, 0.00375 mol) in ammonia-saturated methanol (35 ml) was added yellow mercuric oxide (0.97 g, 0.0045 mol). Stirring was continued for 48 hr, then the solvent evaporated and the black residue boiled with chloroform and filtered. The filtrate was evaporated and the residue recrystallised from ethanol. Yield 0.7 g (62%), m.p. 185-186 °C.
$C_{19}H_{18}N_4$ .0.025$CHCl_3$
Found C 74.94, H 5.96, N 18.41 Expected C 74.83, H 5.95, N 18.35

Example 13
N-(6-Benzylpyrid-2-yl)-N'-(4-chlorophenyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(4-chlorophenyl)thiourea
A mixture of 2-amino-6-benzylpyridine (1.45g, 0.008 mol), 4-chlorophenyl isothiocyanate (1.74g, 0.010 mol) and toluene (10 ml) was refluxed with stirring for 3 hours. The solution was cooled and the product crystallised on treatment with diethyl ether. Yield 1.77 g (59%), m.p. 196-198 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-(4-chlorophenyl)guanidine
A mixture of N-(6-benzylpyrid-2-yl)-N'-(4-chlorophenyl)-thiourea (0.82 g , 0.002 mol), yellow mercuric oxide (0.60 g, 0.003 mol) and methanolic ammonia solution (30 ml) was stirred for 48 hours. The solvent was removed *in vacuo* and the resulting black solid was boiled with chloroform and filtered hot. The pale yellow filtrate was evaporated and triturated with diethyl ether then recrystallised from acetonitrile. Yield 0.34 g (44%), m.p. 214-215 °C.
$C_{19}H_{17}ClN_4$. Found C 67.29, H 5.10, N 16.55 Expected C 67.75, H 5.09, N 16.63

Example 14
N-[6-(4-Methylbenzyl)pyrid-2-yl]-N'-phenylguanidine

(a) 2-Bromo-6-(4-methylbenzyl)pyridine hydrobromide
Powdered zinc (3.59 g, 0.0549 mol) and chlorotrimethylsilane (0.45 g, 0.00422 mol) in dry tetrahydrofuran (80 ml) were stirred under nitrogen for 45 min. a-Bromo-*p*-xylene (7.81 g, 0.0422 mol) in dry tetrahydrofuran (20 ml) was then added dropwise, keeping the temperature below 40 °C (cold water bath). After a further 3 hr, the excess zinc was allowed to settle, and the solution decanted onto 2,6-dibromopyridine (10 g, 0.0422 mol), washing the solid with dry tetrahydrofuran. Tetrakis(triphenylphosphine)palladium(0) (0.49 g, 0.000422mol) was then added, and the mixture heated under nitrogen with stirring at 55 °C for 20 hr. Saturated aqueous ammonium chloride (200 ml) was then added, and the mixture extracted three times with ether. The combined extracts were dried (K_2CO_3) and evaporated to an oil, which was dissolved in a solution of 45% w/v HBr in acetic acid (10 ml). Treatment with ether afforded a crystalline solid which was filtered off, washed and dried. Yield 6.96 g (48%), m.p. 184-187 °C.

(b) 2-Amino-6-(4-methylbenzyl)pyridine maleate
2-Bromo-6-(4-methylbenzyl)pyridine hydrobromide (6.93 g, 0.0202 mol) and 25% aqueous ammonia (50 ml) were heated with stirring at 200 °C in a pressure vessel for 16 hr. The mixture was then made strongly basic with concentrated aqueous sodium hydroxide and extracted three times with chloroform. The combined extracts were dried

(K_2CO_3), evaporated, and treated with ether to give a solid which was filtered off and discarded. The filtrate was evaporated and treated with an ethanol solution of maleic acid (1.1 g, 0.009 mol). The solution was evaporated and the residue triturated with ether then recrystallised from acetonitrile. Yield 1.39 g (22%), m.p. 123-125 °C.

(c) N-[6-(4-Methylbenzyl)pyrid-2-yl]-N'-phenylthiourea

2-Amino-6-(4-methylbenzyl)pyridine maleate (1.37 g, 0.0044 mol) was suspended in water and chloroform and the stirring mixture made basic with conc. aqueous sodium hydroxide. The layers were separated and the aqueous layer again extracted with chloroform. The combined extracts were dried (K_2CO_3) and evaporated, and the residue treated with phenyl isothiocyanate (0.71 g, 0.0052 mol) and toluene (4 ml) and refluxed with stirring for 2.5 hours. The solution was cooled and the product crystallised on treatment with diethyl ether. Yield 0.9 g (62%), m.p. 175-177 °C.

(d) N-[6-(4-Methylbenzyl)pyrid-2-yl]-N'-phenylguanidine

To a suspension of N-[6-(4-Methylbenzyl)pyrid-2-yl]-N'-phenylthiourea (0.89 g , 0.0027 mol) in ammonia-saturated methanol (30 ml) was added yellow mercuric oxide (0.69 g, 0.0032 mol). Stirring was continued for 48 hr, then the solvent evaporated and the black residue boiled with chloroform and filtered. The filtrate was evaporated and the residue recrystallised from acetonitrile. Yield 0.72 g (86%), m.p.156-158 °C.

$C_{20}H_{20}N_4$. Found C 75.95, H 6.32, N 17.69 Expected C 75.92, H 6.37, N 17.71

Example 15

N-[6-(4-Methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine

(a) 2-Bromo-6-(4-methoxybenzyl)pyridine

Powdered zinc (6.62 g, 0.081 mol) and chlorotrimethylsilane (0.88 g, 0.0081 mol) in dry tetrahydrofuran (150 ml) were stirred under nitrogen for 15 min. 4-Methoxybenzyl bromide (16.2 g, 0.081 mol) in dry tetrahydrofuran was then added dropwise, keeping the temperature below 40 °C (cold water bath). After a further 1 hr, the excess zinc was allowed to settle, and the solution decanted onto 2,6-dibromopyridine (12.79 g, 0.054 mol), washing the solid with dry tetrahydrofuran.

Tetrakis(triphenylphosphine)palladium(0) (0.94 g, 0.00081 mol) was then added, and the mixture heated under nitrogen with stirring at 60 °C for 20 hr. Saturated aqueous ammonium chloride (200 ml) was then added, and the mixture extracted three times with ether. The combined extracts were dried (K_2CO_3) and evaporated to an oily solid, which was triturated with ether. The solid was filtered off and discarded, and the filtrate evaporated and purified by flash chromatography (dichloromethane-pet. ether) to give the title compound as an oil. Yield 9 g (60%).

(b) 2-Hydrazino-6-(4-methoxybenzyl)pyridine

A mixture of 2-bromo-6-(4-methoxybenzyl)pyridine (4.75 g, 0.017 mol), hydrazine hydrate (20 ml) and ethanol (40 ml) was placed in a 100 ml pressure vessel and heated at 160 °C for 2.5 hours. The solvent was evaporated and the residue treated with water and basified with sodium hydroxide solution to pH 14. The resultant solid was filtered, washed with water and dried at room temperature, then used immediately without further purification. Yield 2.74 g (70%).

(c) 2-Amino-6-(4-methoxybenzyl)pyridine

A mixture of 2-hydrazino-6-(4-methoxybenzyl)pyridine (3.0 g, 0.013 mol), Raney nickel (ca. 2 spoonfuls) and ethanol (90 ml) was hydrogenated at 50 psi and 50 °C for 1 hour with shaking. The resulting mixture was filtered and the filtrate evaporated to give the product as a solid, which was triturated with ether. Yield 2.13 g (76%), m.p. 113-117 °C.

(d) N-[6-(4-Methoxybenzyl)pyrid-2-yl]-N'-phenylthiourea

A mixture of 2-amino-6-(4-methoxybenzyl)pyridine (1 g, 0.0047 mol), phenyl isothiocyanate (0.76 g, 0.0056 mol) and toluene (5 ml) was refluxed for 2 hours, then diluted with diethyl ether. The white solid was filtered off and washed with ether. Yield 1.13 g (69%), m.p. 172-175 °C.

(e) N-[6-(4-Methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine

To a suspension of N-[6-(4-Methoxybenzyl)pyrid-2-yl]-N'-phenylthiourea (1.12 g , 0.0032 mol) in ammonia-saturated methanol (40 ml) was added yellow mercuric oxide (0.83 g, 0.0039 mol). Stirring was continued for 48 hr, then the solvent evaporated and the black residue boiled with chloroform and filtered. The filtrate was evaporated and the residue crystallised from acetonitrile. Yield 0.86 g (81%), m.p. 160-161 °C.

$C_{20}H_{20}N_4O$. Found C 71.94, H 6.18, N 16.94 Expected C 72.27, H 6.06, N 16.85

Example 16

N-(6-Benzylpyrid-2-yl)-N'-(2-methylphenyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(2-methyphenyl)thiourea

A mixture of 2-amino-6-benzylpyridine (1.05 g, 0.0057mol), *o*-tolyl isothiocyanate (1.02 g, 0.0068 mol) and toluene (5 ml) was refluxed for 2 hours, then diluted with diethyl ether. The white product was filtered off and washed with ether. Yield 1.06 g (56%), m.p. 183-186 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-(2-methylphenyl)guanidine)

A mixture of N-(6-benzylpyrid-2-yl)-N'-(2-methyphenyl)-thiourea (1.08 g , 0.003 mol), yellow mercuric oxide (0.83 g, 0.004 mol) and methanolic ammonia (30 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the resultant

black solid boiled with chloroform (50 ml) and the mixture filtered hot. The filtrate was evaporated and the residue recrystallised from ethanol. Yield 0.34 g (34%), m.p. 184-186 °C.

$C_{20}H_{20}N_4$. Found C 75.69, H 6.46, N 17.73 Expected C 75.92, H 6.37, N 17.71

Example 17

N-(6-Benzylpyrid-2-yl)-N'-(2-chlorophenyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(2-chlorophenyl)thiourea

A mixture of 2-amino-6-benzylpyridine (1.02 g, 0.0055 mol), 2-chlorophenyl isothiocyanate (1.12g, 0.0066 mol) and toluene (5 ml) was refluxed for 2 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether. Yield 1.31 g (67%), m.p. 186-188 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-(2-chlorophenyl)guanidine

A mixture of N-(6-benzylpyrid-2-yl)-N'-(2-chlorophenyl)-thiourea (1.27 g, 0.0036 mol), yellow mercuric oxide (0.93 g, 0.0043 mol) and methanolic ammonia (30 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue boiled with chloroform and filtered hot. The filtrate was evaporated and the residue recrystallised from ethanol. Yield 0.43 g (36%), m.p. 210-211 °C.

$C_{19}H_{17}ClN_4$. Found C 67.66, H 5.23, N 16.60 Expected C 67.75, H 5.09, N 16.63

Example 18

N-(6-Benzylpyrid-2-yl)-N'-(3-methoxyphenyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(3-methoxyphenyl)thiourea

A mixture of 2-amino-6-benzyl pyridine (1.00 g, 0.0054 mol), 3-methoxyphenyl isothiocyanate (1.07 g, 0.0065 mol) and toluene (5 ml) was refluxed for 2 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether. Yield 1.06 g (60%), m.p. 148-150 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-(3-methoxyphenyl)guanidine

A mixture of N-(6-benzylpyrid-2-yl)-N'-(3-methoxyphenyl)-thiourea (1.04 g, 0.003 mol), yellow mercuric oxide (0.74g, 0.0034 mol) and methanolic ammonia (30 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue boiled with chloroform and filtered hot. The filtrate was evaporated and the residue recrystallised from acetonitrile. Yield 0.55 g (56%), m.p.151-153 °C.

$C_{20}H_{20}N_4O$. Found C 72.51, H 6.08, N 16.99 Expected C 72.27, H 6.06, N 16.85

Example 19

N-[6-(3-Methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine

(a) 2-Bromo-6-(3-methoxybenzyl)pyridine

Powdered zinc (8.13 g, 0.124 mol) and chlorotrimethylsilane (1.08 g, 0.01 mol) in dry tetrahydrofuran (175 ml) were stirred under nitrogen for 15 min. 3-Methoxybenzyl bromide (19.9 g, 0.1 mol) was then added dropwise, keeping the temperature below 40 °C (cold water bath). After a further 1 hr, the excess zinc was allowed to settle, and the solution decanted onto 2,6-dibromopyridine (15.71 g, 0.0663 mol), washing the solid with dry tetrahydrofuran. Tetrakis(triphenylphosphine)palladium(0) (0.77 g, 0.00066 mol) was then added, and the mixture stirred at room temperature under nitrogen for 20 hr. Saturated aqueous ammonium chloride was then added, and the mixture extracted three times with ether. The combined extracts were dried (K_2CO_3) and evaporated to an oily solid, which was triturated with dichloromethane. The solid was filtered off and discarded, and the filtrate evaporated and purified by flash chromatography (dichloromethane-pet. ether) to give the title compound as an oil. Yield 12.78 g (69%).

(b) 2-Hydrazino-6-(3-methoxybenzyl)pyridine

A mixture of 2-bromo-6-(3-methoxybenzyl)pyridine (12.77 g, 0.0442 mol), hydrazine hydrate (30 ml) and ethanol (60 ml) was placed in a 250 ml pressure vessel and heated at 160 °C for 2.5 hours. The solvent was evaporated and the residue treated with water and basified with sodium hydroxide solution to pH 14. The oil which separated was extracted into dichloromethane, washed with water, dried (K_2CO_3) and evaporated. Yield 9.72 g (96%).

(c) 2-Amino-6-(3-methoxybenzyl)pyridine

A mixture of 2-hydrazino-6-(3-methoxybenzyl)pyridine (9.7 g, 0.0423 mol), Raney nickel (ca. 1 spoonful) and ethanol (100 ml) was hydrogenated at 50 psi and 50 °C for 2 hours with shaking. The resulting mixture was filtered, the filtrate was evaporated and the product crystallised from ether-pet. ether. Yield 7.14 g (79%), m.p. 80-82 °C.

(d) N-[6-(3-Methoxybenzyl)pyrid-2-yl]-N'-phenylthiourea

A stirring mixture of 2-amino-6-(3-methoxybenzyl)pyridine (1.07 g, 0.005 mol) and phenyl isothiocyanate (0.81 g, 0.006 mol) in toluene (8 ml) was heated under reflux with stirring for 2 hr. After allowing to cool, the solution was treated with ether, and the resulting solid filtered off, washed and dried. Yield 1.0 g (57%), m.p. 142-145 °C.

(e) N-[6-(3-Methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine

To a suspension of N-[6-(3-methoxybenzyl)pyrid-2-yl]-N'-phenylthiourea (0.98 g , 0.0028 mol) in ammonia-saturated methanol (40 ml) was added yellow mercuric oxide (0.73g, 0.0034 mol). Stirring was continued for 3 days, then the solvent evaporated and the black

residue boiled with chloroform and filtered. The filtrate was evaporated and the residue recrystallised twice from acetonitrile.
Yield 0.59 g (63%), m.p. 166-168 °C.
$C_{20}H_{20}N_4O$. Found C 72.14, H 6.05, N17.01 Expected C 72.27, H 6.06, N 16.85

Example 20
N-(6-Benzylpyrid-2-yl)-N'-(3-chlorophenyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(3-chlorophenyl)thiourea
A mixture of 2-amino-6-benzyl pyridine (1.02g, 0.0055 mol), 3-chlorophenyl isothiocyanate (1.13g, 0.0066 mol) and toluene (5 ml) was refluxed for 3.5 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether. Yield 1.61 g (83%), m.p. 187-189 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-(3-chlorophenyl)guanidine
A mixture of N-(6-benzylpyrid-2-yl)-N'-(3-chlorophenyl)-thiourea (1.58g, 0.0044 mol), yellow mercuric oxide (1.18g, 0.0054 mol) and methanolic ammonia (30 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue triturated with ether to give a crystalline solid. Yield 0.78 g (52%), m.p. 131-133 °C.
$C_{19}H_{17}ClN_4$. Found C 67.70, H 5.25, N 16.57 Expected C 67.75, H 5.09, N 16.63

Example 21
N-(6-Benzylpyrid-2-yl)-N'-(4-methoxyphenyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(4-methoxyphenyl)thiourea
A mixture of 4-methoxyphenyl isothiocyanate (1.16g, 0.006 mol), 2-amino-6-benzylpyridine (1.04 g, 0.0056 mol) and toluene (5 ml) was refluxed for 3.5 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether.
Yield 1.52 g (77%), m.p. 176-179 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-(4-methoxyphenyl)guanidine
A mixture of N-(6-benzylpyrid-2-yl)-N'-(4-methoxyphenyl)-thiourea (1.48g, 0.0042 mol), yellow mercuric oxide (1.11 g, 0.0051 mol), and methanolic ammonia (30 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue recrystallised from acetonitrile. Yield 0.58 g (48%), m.p. 151-153 °C.
$C_{20}H_{20}N_4O$. Found C 72.21, H 6.13, N 16.90 Expected C 72.27, H 6.06, N 16.85

Example 22

N-(2-Benzyl-3-methoxypyrid-6-yl)-N'-phenylguanidine

(a) 2-Bromo-3-methoxy-6-phthalimidopyridine

A mixture of 2-bromo-3-methoxy-6-aminopyridine (1.8 g, 8.9 mmol) and phthalic anhydride (1.48 g, 10 mmol) in toluene (100 ml) was stirred at reflux for 16 hours with azeotropic removal of water. After evaporation of the solvent, aqueous sodium bicarbonate was added and the product extracted into dichloromethane, dried, and the solvent evaporated. The residue was recrystallised from ethanol. Yield 2.74 g (93%), m.p. 230-231 °C.

(b) 2-Benzyl-3-methoxy-6-phthalimidopyridine

A mixture of 2-bromo-3-methoxy-6-phthalimidopyridine (2.7 g, 8.2 mmol), benzylzinc bromide (24 ml of 0.5M solution in THF) and tetrakis(triphenylphosphine)palladium(0) (0.09 g, 0.08 mmol) was stirred at room temperature for 2 days, then quenched with aqueous ammonium chloride. The product was extracted into a mixture of ether and 2-propanol, dried, and the solvent evaporated. Trituration with ether gave the desired product. Yield 0.74 g (27%), m.p. 180-185 °C.

(c) 2-Benzyl-3-methoxy-6-aminopyridine

A solution of 2-benzyl-3-methoxy-6-phthalimidopyridine (0.70 g, 2 mmol) and hydrazine hydrate (0.29 ml, 3 mmol) in ethanol (5 ml) was stirred at reflux for 75 min. After evaporation of the solvent, the residue was triturated with ether, and the solid filtered off and discarded. The filtrate was purified by chromatography (silica, 4% methanol in dichloromethane) to obtain the product as a dark gum. Yield 0.38 g (98%).

(d) N-(2-Benzyl-3-methoxypyrid-6-yl)-N'-phenylthiourea

A mixture of 2-benzyl-3-methoxy-6-aminopyridine (0.34 g, 1.7 mmol) and phenyl isothiocyanate (0.24 ml, 2 mmol) in toluene (5 ml) was stirred at reflux for 4.5 hours. Evaporation of the solvent and trituration with methanol gave the product.
Yield 0.38 g, m.p. 163-166 °C.

(e) N-(2-Benzyl-3-methoxypyrid-6-yl)-N'-phenylguanidine

A mixture of N-(2-benzyl-3-methoxypyrid-6-yl)-N'-phenyl-thiourea (0.38 g, 1.1 mmol) and mercuric oxide (0.28 g, 1.3 mmol) in methanolic ammonia (15 ml) was stirred at room temperature for 2 days, then filtered through celite. The filtrate was evaporated and the residue recrystallised from ethanol. Yield 0.15 g (41%), m.p. indeterminate.
$C_{20}H_{20}N_4O$ .0.15H_2O
Found C 71.67, H 6.10, N 16.65 Requires C 71.68, H 6.11, N 16.72

Example 23

N-[6-(4-Fluorobenzyl)pyrid-2-yl]-N'-phenylguanidine

(a) 2-Bromo-6-(4-fluorobenzyl)pyridine

Powdered zinc (4.09 g, 0.063 mol) and chlorotrimethylsilane (0.63 ml, 0.005 mol) in dry tetrahydrofuran (100 ml) were stirred under nitrogen for 20 min. 4-Fluorobenzyl bromide (9.45 g, 0.05 mol) was then added dropwise, keeping the temperature below 40 °C (cold water bath). After a further 1 hr, the excess zinc was allowed to settle, and the solution decanted onto 2,6-dibromopyridine (7.9 g, 0.033 mol), washing the solid with dry tetrahydrofuran. Tetrakis(triphenylphosphine)palladium(0) (0.38 g, 0.00033 mol) was then added, and the mixture stirred at room temperature under nitrogen for 2 days. Saturated aqueous ammonium chloride was then added, and the mixture extracted three times with ether. The combined extracts were dried ($MgSO_4$) and evaporated, and the residue purified by flash chromatography (dichloromethane-pet. ether) to give the title compound as an oil. Yield 4.5 g (34%).

(b) 2-Hydrazino-6-(4-fluorobenzyl)pyridine

A mixture of 2-bromo-6-(4-fluorobenzyl)pyridine (4.4 g, 0.0165 mol), hydrazine hydrate (12 ml) and ethanol (40 ml) was placed in a 100 ml pressure vessel and heated at 160 °C for 2.5 hours. The solvent was evaporated and the residue treated with water and basified with sodium hydroxide solution to pH 14. The oil which separated soon crystallised and was filtered off, washed and dried, then used immediately without further purification. Yield 3.46 g (97%).

(c) 2-Amino-6-(4-fluorobenzyl)pyridine

A mixture of 2-hydrazino-6-(4-fluorobenzyl)pyridine (3.45 g, 0.0159 mol), Raney nickel (ca. 1 spoonful) and ethanol (100 ml) was hydrogenated at 50 psi and 50°C for 2 hour with shaking. The resulting mixture was filtered through celite, the filtrate evaporated and the product crystallised under pet. ether (b.p. 40-60). Yield 2.66 g (83%), m.p. 69-71 °C.

(d) N-[6-(4-fluorobenzyl)pyrid-2-yl]-N'-phenylthiourea

A stirring mixture of 2-amino-6-(4-fluorobenzyl)pyridine (1.3 g, 0.0064 mol) and phenyl isothiocyanate (1.04 g, 0.0077 mol) in toluene (8 ml) was heated under reflux with stirring for 3.5 hr. After allowing to cool, the solution was treated with ether, and the resulting solid filtered off, washed and dried. Yield 1.46 g (68%), m.p. 198-200°C.

(e) N-[6-(4-Fluorobenzyl)pyrid-2-yl]-N'-phenylguanidine

To a suspension of N-[6-(4-fluorobenzyl)pyrid-2-yl]-N'-phenylthiourea (1.43 g, 0.0042 mol) in ammonia-saturated methanol (40 ml) was added yellow mercuric oxide (1.1 g, 0.0051 mol). Stirring was continued for 2 days, then the solvent was evaporated and the black residue boiled with chloroform and filtered through celite. The filtrate was evaporated and the residue recrystallised from acetonitrile.

Yield 0.82 g (60%), m.p. 128-130 °C.

$C_{19}H_{17}FN_4$. Found C 71.29, H 5.53, N 17.62 Expected C 71.23, H 5.35, N 17.49

Example 24
N-[6-(4-Nitrobenzyl)pyrid-2-yl]-N'-phenylguanidine

(a) 2-Bromo-6-(4-nitrobenzyl)pyridine
To a nitrating mixture of concentrated nitric acid (8 ml) and concentrated sulphuric acid (8 ml) was added with stirring 2-bromo-6-benzylpyridine (5 g, 0.0202 mol), keeping the temperature at 10-20°C. The reaction was stirred at room temperature for 1 hr, then poured onto ice and neutralised by the addition of solid ammonium carbonate. The mixture was extracted three times with ether, and the combined extracts dried ($MgSO_4$) and evaporated to an oil, which crystallised from ethyl acetate-pet. ether. The product was filtered off, washed and dried. Yield 2.54 g (43%), m.p. 78-80 °C.

(b) 2-Hydrazino-6-(4-nitrobenzyl)pyridine
A mixture of 2-bromo-6-(4-nitrobenzyl)pyridine (2.53 g, 0.0086 mol), hydrazine hydrate (7 ml) and ethanol (40 ml) was placed in a 100 ml pressure vessel and heated at 160 °C for 2 hours. The solvent was evaporated and the residue treated with water and basified with sodium hydroxide solution to pH 14. The resulting yellow solid was filtered off and recrystallised from acetonitrile. Yield 1.38 g (65%), m.p. 139-141 °C.

(c) 2-Azido-6-(4-nitrobenzyl)pyridine
To a stirring suspension of 2-hydrazino-6-(4-nitrobenzyl)-pyridine (1.37 g, 0.0056 mol) in concentrated hydrochloric acid (50 ml) was added at 0-5°C sodium nitrite (3.87 g, (0.056 mol). The mixture was allowed to warm to room temperature and stirred for a further hour. Dilution with water followed by neutralisation with concentrated aqueous sodium hydroxide gave the product as a solid. Yield 1.38 g (97%), m.p. 188-190 °C.

(d) 2-[(Triphenylphosphoranylidene)amino]-6-(4-nitrobenzyl)pyridine
A stirring mixture of 2-azido-6-(4-nitrobenzyl)pyridine (2.37 g, 0.0093 mol) and triphenylphosphine (2.68 g, 0.0102 mol) in dioxan (45 ml) was heated under reflux for 3 hr. The solvent was evaporated and the residue treated with ether. The product soon crystallised, and was filtered off, washed and dried. Yield 4.4 g (97%), m.p. 147-149 °C.

(e) N-[6-(4-Nitrobenzyl)pyrid-2-yl]-N'-phenylguanidine
A solution of 2-[(triphenylphosphoranylidene)amino]-6-(4-nitrobenzyl)pyridine (1.2 g, 0.0025 mol) in dry tetrahydrofuran (20 ml) was treated with phenyl isocyanate (0.29 g, 0.0025 mol) and stirred for 3 hr. More phenyl isocyanate (0.15 g, 0.0012 mol) was added, and the reaction left to stand for 16 hr. Ammonia gas was then passed through the solution with stirring for 10 min, and after a further 20 min, the solvent was evaporated off, and the residue purified by flash chromatography (methanolic ammonia-dichloromethane) and recrystallisation from acetonitrile.

Yield 0.3 g (35%), m.p. 185-187 °C.
$C_{19}H_{17}N_5O_2$. Found C 65.62, H 5.06, N 20.15 Expected C 65.70, H 4.93, N 20.16

Example 25

N-[6-(4-Aminophenylmethyl)pyrid-2-yl]-N'-phenylguanidine

A mixture of N-[6-(4-nitrophenylmethyl)pyrid-2-yl]-N'-phenylguanidine (0.65 g, 0.0019 mol) and 10% palladium on carbon catalyst (0.1 g) in ethanol was hydrogenated at 40 p.s.i. for 2 hr. The catalyst was filtered off and the filtrate evaporated to low volume to induce crystallisation. Yield 0.46 g (78%), m.p. 203-205 °C (dec).
$C_{19}H_{19}H_5$. Found C 71.71, H 6.21, N 21.99 Expected C 71.90, H 6.03, N 22.06

Example 26

N-(6-Benzylpyrid-2-yl)-N'-(4-cyanophenyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(4-cyanophenyl)thiourea
A mixture of 4-cyanophenyl isothiocyanate (1.04 g, 0.006 mol), 2-amino-6-benzylpyridine (1.00 g, 0.0054 mol) and toluene (10 ml) was refluxed for 3.5 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether.
Yield 1 g (53%), m.p. 207-209 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-(4-cyanophenyl)guanidine
A mixture of N-(6-benzylpyrid-2-yl)-N'-(4-cyanophenyl)thiourea (0.98 g, 0.003 mol), yellow mercuric oxide (0.74 g, .0034 mol), and methanolic ammonia (40 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue recrystallised from acetonitrile Yield 0.53 g (57%), m.p. 200-201 °C.
$C_{20}H_{17}N_5$. Found C 73.46, H 5.38, N 21.41 Expected C 73.37, H 5.23, N 21.39

Example 27

N-[6-(Benzylpyrid-2-yl)]-N'-(4-methylthiophenyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(4-methylthiophenyl)thiourea
A mixture of 4-methylthiophenyl isothiocyanate (5.9 g, 27.1 mmol), 2-amino-6-benzylpyridine (5.0 g, 27.1 mmol) and toluene (150 ml) was refluxed for 3.5 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether.
Yield 6.35 g (64%).

(b) N-(6-Benzylpyrid-2-yl)-N'-(4-methylthiophenyl)guanidine
A mixture of N-(6-benzylpyrid-2-yl)-N'-(4-methylthiophenyl)thiourea (6.2 g, 16.9 mmol), yellow mercuric oxide (4.4 g, 20.3 mmol), and methanolic ammonia (400 ml) was stirred

for 72 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue recrystallised from acetonitrile. Yield 3.2 g (55%), m.p. 192-194 °C.
$C_{20}H_{20}N_4S$. Found C 68.92, H 5.84, N 16.07 Requires C 68.94, H 5.79, N 16.08

Example 28
N-[6-(Benzylpyrid-2-yl)]-N'-(4-methylsulphonylphenyl)guanidine 3-chlorobenzoate salt

A solution of N-(6-benzylpyrid-2-yl)-N'-(4-methylthio-phenyl)guanidine (1.0 g, 2.9 mmol) in dichloromethane (50 ml) was maintained at -35 to -45 °C as a solution of *m*-chloroperbenzoic acid (0.59 g, 3.4 mmol) was added dropwise with stirring. After a further 2 hours at this temperature, the solution was allowed to warm to room temperature, and stirring was continued for 1 hour. Aqueous sodium bicarbonate was added, and the organic layer was washed with water, dried and evaporated. The residual oil was found to consist mainly of sulphone, with only minor amounts of sulphoxide. Chromatography (silica, 5% methanol in chloroform) gave the pure product.
Yield 0.35 g (34%), m.p. 175-178 °C.
$C_{20}H_{20}N_4O_2S \cdot C_7H_5ClO_2 \cdot 0.3H_2O$
Found C 59.69, H 4.74, N 10.33, S 6.09 Requires C 59.78, H 4.76, N 10.33, S 5.91

Example 29
N-[6-(4-Methoxybenzyl)-5-methoxypyrid-2-yl]-N'-phenylguanidine

(a) 2-(4-Methoxybenzyl)-3-methoxy-6-phthalimidopyridine
Powdered zinc (1.23 g, 0.0188 mol) and chlorotrimethylsilane (0.11 g, 0.001 mol) in dry tetrahydrofuran (20 ml) were stirred under nitrogen for 15 min. 4-Methoxybenzyl bromide (3 g, 0.015 mol) was then added dropwise, keeping the temperature below 40 °C (cold water bath). After a further 1 hr, the excess zinc was allowed to settle, and the solution decanted onto 2-bromo-3-methoxy-6-phthalimido-pyridine (3.33 g, 0.01 mol), washing the solid with dry tetrahydrofuran. Tetrakis(triphenylphosphine)palladium(0) (0.22 g, 0.0002 mol) was then added, and the mixture heated at 55 °C under nitrogen for 20 hr. The mixture was then treated with saturated aqueous ammonium chloride, and extracted three times with ether. The combined extracts were dried (K_2CO_3) and evaporated, and the residue purified by flash chromatography (ethyl acetate-dichloromethane). The product was triturated with ether.
Yield 2.06 g (55%), m.p. 133-135 °C.

(b) 2-(4-Methoxybenzyl)-3-methoxy-6-aminopyridine

2-(4-Methoxybenzyl)-3-methoxy-6-phthalimidopyridine (1.96 g, 0.0052 mol) and hydrazine hydrate (0.79 ml, 0.016 mol) in ethanol (20 ml) were refluxed with stirring for 1 hr. After allowing to cool, the precipitated solid was filtered off and discarded. The filtrate was evaporated to a solid, which was triturated with ether.

Yield 1.08 g (84%), m.p. 110-112 °C.

(c) N-[6-(4-Methoxybenzyl)-5-methoxypyrid-2-yl]-N'-phenylthiourea

A stirring mixture of 2-(4-methoxybenzyl)-3-methoxy-6-aminopyridine (1.07 g, 0.0044 mol) and phenyl isothiocyanate (0.71 g, 0.0053 mol) in toluene (10 ml) was heated under reflux with stirring for 2.5 hr. After allowing to cool, the solution was treated with ether, and the resulting solid filtered off, washed and dried.

Yield 1.09 g (66%), m.p. 165-167 °C.

(d) N-[6-(4-Methoxybenzyl)-5-methoxypyrid-2-yl]-N'-phenylguanidine

To a suspension of N-[6-(4-methoxybenzyl)-5-methoxypyrid-2-yl]-N'-phenylthiourea (0.5 g , 0.0013 mol) in ammonia-saturated methanol (15 ml) was added yellow mercuric oxide (0.34 g, 0.0016 mol). Stirring was continued for 2 days, then the solvent evaporated and the black residue boiled with chloroform and filtered through celite. The filtrate was evaporated and the residue recrystallised from acetonitrile.

Yield 0.28 g (58%), m.p. 152-154 °C.

$C_{21}H_{22}N_4O_2$. Found C 69.34, H 6.18, N 15.38 Expected C 69.59, H 6.12, N 15.46

Example 30

N-[6-(4-Methoxybenzyl)pyrid-2-yl]-N'-methylguanidine maleate

(a) N-[6-(4-Methoxybenzyl)pyrid-2-yl]-N'-methylthiourea

A stirring mixture of 2-amino-6-(4-methoxybenzyl)pyridine (1.08 g, 0.005 mol) and methyl isothiocyanate (0.44 g, 0.0061 mol) in toluene (5 ml) was heated under reflux with stirring for 1 hr. A further quantity of methyl isothiocyanate (0.44 g, 0.0061 mol) was added, and reflux continued for another 2 hr. After allowing to cool, the solution was treated with ether, and the resulting solid filtered off, washed and dried.

Yield 0.88 g (61%), m.p. 157-160 °C.

(b) N-[6-(4-Methoxybenzyl)pyrid-2-yl]-N'-methylguanidine maleate

To a stirring suspension of N-[6-(4-methoxybenzyl)pyrid-2-yl]-N'-methylthiourea (0.86 g, 0.003 mol) in ammonia-saturated methanol (40 ml) was added yellow mercuric oxide (0.78 g, 0.0036 mol). Stirring was continued for 2 days, then the solvent evaporated and the black residue boiled with chloroform and filtered through celite. The filtrate was evaporated to an oil, which was dissolved in a solution of maleic acid (0.36 g) in ethanol. The product soon crystallised. Yield 0.92 g (79%), m.p. 162-164 °C.

$C_{15}H_{18}N_4O.C_4H_4O_4$
Found C 58.99, H 5.76, N 14.48 Expected C 59.06, H 5.74, N 14.50

Example 31
N-[6-(Benzylpyrid-2-yl)]-N'-(2-pyrimidyl)guanidine

(a) 6-Benzylpyrid-2-yl isothiocyanate
A mixture of 2-amino-6-benzylpyridine (0.82 g, 4.45 mmol) and dipyrid-2-yl thiocarbonate (1.03 g, 4.45 mmol) in acetonitrile (20 ml) was treated with 4-dimethylaminopyridine, and stirred for 2 hours at room temperature. The solvent was evaporated, and the residue was taken up in dichloromethane, washed with water, dried, and the dichloromethane evaporated. Yield 0.63 g (63%).

(b) N-[6-(Benzylpyrid-2-yl)]-N'-(2-pyrimidyl)thiourea
A mixture of 6-benzylpyrid-2-yl isothiocyanate (0.5 g, 2.21 mmol) and 2-aminopyrimidine (0.175 g, 1.84 mmol) in toluene (20 ml) was stirred under reflux for 16 hours, then allowed to cool. The product was filtered off and washed with ether. Yield 0.45 g (76%).

(c) N-[6-(Benzylpyrid-2-yl)]-N'-(2-pyrimidyl)guanidine
A mixture of yellow mercuric oxide (0.32 g, 1.25 mmol), N-(6-benzylpyrid-2-yl)-N'-(2-pyrimidyl)thiourea (0.40 g, 1.29 mmol) and methanolic ammonia (20 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue recrystallised from acetonitrile. Yield 0.28 g (76%), m.p. 140-142 °C.
$C_{17}H_{16}N_6 .H_2O$. Found C 63.39, H 5.20, N 25.85 Requires C 63.33, H 5.62, N 26.07

Example 32
N-(6-Benzylpyrid-2-yl)-N'-benzylguanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-benzylthiourea
A mixture of 2-amino-6-benzylpyridine (1.01 g, 0.0055 mol), benzyl isothiocyanate (0.98 g, 0.0066 mol) and toluene (5 ml) was refluxed for 3.5 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether. Yield 1.49 g (82%), m.p. 142-144 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-benzylguanidine
A mixture of yellow mercuric oxide (1.15g, 0.0053 mol), N-(6-benzylpyrid-2-yl)-N'-benzylthiourea (1.47g, 0.0044 mol) and methanolic ammonia (35 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was

boiled with chloroform and filtered hot. The filtrate was evaporated and the residue recrystallised from ether-pet. ether. Yield 0.66 g (47%), m.p. 83-84 °C.
$C_{20}H_{20}N_4$. Found C 75.67, H 6.46, N 17.79 Expected C 75.92, H 6.37, N 17.71

Example 33
N-[6-(Benzylpyrid-2-yl)]-N'-(2-thiazolyl)guanidine

(a) N-[6-(Benzylpyrid-2-yl)]-N'-(2-thiazolyl)thiourea
A mixture of 6-benzylpyrid-2-yl isothiocyanate (1.72 g, 7.61 mmol) and 2-aminopyrimidine (0.634 g, 6.34 mmol) in toluene (80 ml) was stirred under reflux for 16 hours, then allowed to cool. The white crystalline product was filtered off and washed with ether. Yield 1.41 g (76%), m.p. 219-222 °C.

(b) N-[6-(Benzylpyrid-2-yl)]-N'-(2-thiazolyl)guanidine
A mixture of yellow mercuric oxide (1.23 g, 5.71 mmol), N-(6-benzylpyrid-2-yl)-N'-(2-thiazolyl)thiourea (1.40 g, 4.16 mmol) and methanolic ammonia (50 ml) was stirred for 16 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot, then the solvent was evaporated.
Yield 0.78 g (53%), m.p. 163-166 °C.
$C_{16}H_{15}N_5S$. Found C 61.78, H 4.94, N 22.36 Requires C 62.11, H 4.89, N 22.64

Example 34
N-[6-(Benzylpyrid-2-yl)]-N'-(2-pyrazinyl)guanidine

(a) N-[6-(Benzylpyrid-2-yl)]-N'-(2-pyrazinyl)thiourea
A mixture of 6-benzylpyrid-2-yl isothiocyanate (1.3 g, 5.75 mmol) and 5-aminopyrimidine (0.45 g, 4.79 mmol) in toluene (50 ml) was stirred under reflux for 48 hours, then allowed to cool and the solid filtered off and washed with ether. Yield 0.69 g (38%), m.p. 180-183 °C.

(b) N-[6-(Benzylpyrid-2-yl)]-N'-(2-pyrazinyl)guanidine
A mixture of yellow mercuric oxide (0.58 g, 2.58 mmol), N-(6-benzylpyrid-2-yl)-N'-(2-pyrazinyl)thiourea (0.69 g, 2.15 mmol) and methanolic ammonia (80 ml) was stirred for 24 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot, then the filtrate was evaporated, and the residue purified by chromatography (silica gel, 5% methanolic ammonia in dichloromethane) and recrystallisation from acetonitrile.
Yield 0.42 g (64%), m.p. 160-162 °C.
$C_{17}H_{16}N_6$. Found C 66.85, H 5.39, N 27.45 Requires C 67.09, H 5.30, N 27.61

Example 35
N-(6-Benzylpyrid-2-yl)-N'-(5-pyrimidyl)guanidine

(a) N-[6-(Benzylpyrid-2-yl)]-N'-(5-pyrimidyl)thiourea
A mixture of 6-benzylpyrid-2-yl isothiocyanate (1.1 g, 4.86 mmol) and 5-aminopyrimidine (0.38 g, 4.05 mmol) in toluene (50 ml) was stirred under reflux for 20 hours, then the solvent was evaporated and the residue triturated with ether/pet. ether. The resulting solid was purified by chromatography (silica gel, chloroform).
Yield 0.35 g (22%).

(b) N-[6-(Benzylpyrid-2-yl)]-N'-(5-pyrimidyl)guanidine
A mixture of yellow mercuric oxide (0.24 g, 1.12 mmol), N-(6-benzylpyrid-2-yl)-N'-(5-pyrimidyl)thiourea (0.30 g, 0.93 mmol) and methanolic ammonia (50 ml) was stirred for 72 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot, then the filtrate was evaporated, and the residue purified by chromatography (silica gel, 0-10% methanol in chloroform) and recrystallisation from acetonitrile. Yield 0.18 g (64%), m.p. 178-181 °C.
$C_{17}H_{16}N_6$. Found C 67.25, H 5.41, N 27.60 Requires C 67.09, H 5.30, N 27.61

Example 36
N-(6-Benzylpyrid-2-yl)-N'-(3-methoxypropyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-3-methoxypropylthiourea
A mixture of 2-amino-6-benzylpyridine (1.6 g, 0.0087 mol), 3-methoxypropyl isothiocyanate (1.37 g, 0.01 mol) and toluene (10 ml) was refluxed for 6.5 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether.
Yield 1.51 g (55%), m.p. 92-94 °C.

(b) N-(6-Benzyl-pyrid-2-yl)-N'-3-methoxypropylguanidine
A mixture of N-(6-benzylpyrid-2-yl)-N'-3-methoxypropyl-thiourea (1.49 g, 0.005 mol), yellow mercuric oxide (1.32 g, 0.006 mol) and methanolic ammonia (45 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue triturated with ether then recrystallised twice from acetonitrile.
Yield 0.36 g (26%), m.p. 107-109 °C.
$C_{17}H_{22}N_4O$. Found C 68.45, H 7.34, N 18.83 Expected C 68.43, H 7.43, N 18.78

Example 37
N-(6-Benzylpyrid-2-yl)-N'-cyclohexylguanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(cyclohexyl)thiourea
A mixture of 2-amino-6-benzylpyridine (2.01 g, 0.011 mol), cyclohexyl isothiocyanate (1.84 g, 0.013 mol) and toluene (10 ml) was refluxed for 6 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether. Yield 2.0 g (57%).

(b) N-(6-Benzyl pyrid-2-yl)-N'-(cyclohexyl)guanidine
A mixture of N-(6-benzylpyrid-2-yl)-N'-(cyclohexyl)thiourea (1.95 g, 0.006 mol), yellow mercuric oxide (1.56 g, 0.007 mol) and methanolic ammonia (45 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue purified by flash chromatography (silica, 5% methanol in dichloromethane) to give the product as an oil. Yield 1.0 g (54%).
$C_{19}H_{24}N_4 . 0.25 H_2O$
Found C 72.94, H 7.80, N 17.73 Expected C 72.92, H 7.89, N 17.91

Example 38
N-(6-Benzylpyrid-2-yl)-N'-(2-methoxyethyl)guanidine

(a) N-(6-Benzylpyrid-2-yl)-N'-(2-methoxyethyl)thiourea)
A mixture of 2-amino-6-benzylpyridine (1.52 g, 0.008 mol), 2-methoxyethyl isothiocyanate (1.14 g, 0.009 mol) and toluene (10 ml) was refluxed for 6 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether. Yield 1.25 g (51%), m.p. 89-91 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-(2-methoxyethyl)guanidine
A mixture of N-(6-benzylpyrid-2-yl)-N'-(2-methoxyethyl)-thiourea (1.24 g, 0.003 mol), yellow mercuric oxide (0.86 g, 0.004 mol) and methanolic ammonia (45 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue purified by flash chromatography (methanol-ammonia/dichloromethane) to give the product as an oil. Yield 0.84 g (73%).
$C_{16}H_{20}N_4O$. Found C 67.43, H 7.14, N 19.54 Expected C 67.58, H 7.09, N 19.70

Example 39
N-[(6-Benzyl)pyrid-2-yl]-N'-butylguanidine

(a) N-(6-Benzyl pyrid-2-yl)-N'-butylthiourea
A mixture of 2-amino-6-benzylpyridine (1.50 g, 0.008 mol), n-butyl isothiocyanate (1.12 g, 0.009 mol) and toluene (10 ml) was refluxed for 5.5 hours, cooled and treated with diethyl ether. The product was filtered off and washed with ether.

Yield 1.51 g (62%), m.p.100-102 °C.

(b) N-(6-Benzylpyrid-2-yl)-N'-butylguanidine

A mixture of N-(6-benzylpyrid-2-yl)-N'-butylthiourea (1.49 g, 0.005 mol), yellow mercuric oxide (1.31 g, 0.006 mol) and methanolic ammonia (45 ml) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue purified by flash chromatography (silica, 5-20% methanolic ammonia in dichloromethane). The product crystallised on treatment with petroleum ether.

Yield 0.54 g (39%), m.p. 54-56 °C.

$C_{17}H_{22}N_4 .0.1HCl .0.1H_2O$

Found C 70.83, H 7.69, N 19.40, Cl 1.03 Expected C 70.94, H 7.81, N 19.47, Cl 1.23

Example 40

N-(6-Benzylpyrid-2-yl)-N'-methyl-N'-phenylguanidine maleate

(a) N-(6-Benzylpyrid-2-yl)-N'-benzoylthiourea

To a suspension of 2-amino-6-benzylpyridine (1 g, 0.0054 mol) in ether (20 ml) was added benzoyl isothiocyanate (0.97 g, 0.006 mol). After 2 hr, the mixture was diluted with pet. ether and the resulting solid filtered off, washed and dried.

Yield 1.76 g (93%), m.p.138-140 °C.

(b) N-(6-Benzylpyrid-2-yl)thiourea

To a stirring suspension of N-(6-benzylpyrid-2-yl)-N'-benzoylthiourea (1.05 g, 0.003 mol) in ethanol (6 ml) was added a solution of sodium hydroxide (0.24 g, 0.006 mol) in water (4 ml). The mixture was refluxed for 1 hr, then cooled, neutralised with glacial acetic acid, and treated with 25% aqueous ammonia. The resulting solid was filtered off, washed and dried. Yield 0.64 g (88%), m.p. 216-218 °C.

(c) N-(6-Benzylpyrid-2-yl)-S-methylthiouronium iodide

N-(6-Benzylpyrid-2-yl)thiourea (0.63 g, 0.0026 mol) and iodomethane (2 ml) were heated under reflux with stirring for 1 hr. The solvent was evaporated but the reaction was incomplete, hence the residue was dissolved in ethanol (10 ml), treated with iodomethane (2 ml) and refluxed for a further 0.5 hr. The solvent was evaporated,and the resulting solid triturated with ether and filtered, washed and dried.

Yield 0.93 g (93%), m.p. 208-211 °C (dec).

(d) N-(6-Benzylpyrid-2-yl)-N'-methyl-N'-phenylguanidine maleate

N-(6-Benzylpyrid-2-yl)-S-methylthiouronium iodide (0.92 g, 0.0024 mol) was shaken with aqueous sodium bicarbonate and dichloromethane until complete solution was obtained. The layers were separated, the aqueous layer extracted again with dichloromethane, and the combined extracts dried (K_2CO_3) and evaporated. The resulting

oil was fused at 190 °C with N-methylaniline (0.31 g, 0.0029 mol) for 40 min, then allowed to cool. The reaction mixture was purified by flash chromatography (ammoniacal methanol-dichloromethane) to give the product as an oil. Treatment with maleic acid (0.12 g) and recrystallisation from dichloromethane-ether gave the compound as the maleate salt, yield 0.22 g (21%), m.p. 122-124 °C.

$C_{20}H_{20}N_4 .C_4H_4O_4$

Found C 66.44, H 5.66, N 12.98 Expected C 66.65, H 5.59, N 12.95

Example 41

N-(6-Benzylpyrid-2-yl)-N'-methyl-N''-phenylguanidine

A mixture of yellow mercuric oxide (0.9 g, 0.004 mol), N-(6-Benzylpyrid-2-yl)-N'-phenylthiourea (1.11 g , 0.003 mol) and methylamine (35 ml of 33% w/w solution in IMS) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue triturated with ether, then recrystallised from acetonitrile.

Yield 0.26 g (24%), m.p. 106-107 °C.

$C_{20}H_{20}N_4$. Found C 75.78, H 6.40, N 17.85 Expected C 75.92, H 6.37, N 17.71

Example 42

N-(6-Benzylpyrid-2-yl)-N',N'-dimethyl-N''-phenylguanidine

A mixture of N-(6-benzylpyrid-2-yl)-N'-phenylthiourea (0.69 g, 0.0022 mol), yellow mercuric oxide (0.57 g, 0.0026 mol) and dimethylamine (40 ml of a 33% w/w solution in ethanol) was stirred at room temperature for 3 days. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue recrystallised from aqueous acetonitrile.

Yield 0.16 g (23%), m.p. 86-88 °C.

$C_{21}H_{22}N_4$. Found C 76.10, H 6.71, N 17.00 Expected C 76.33, H 6.71, N 16.96

Example 43

N-[6-(3-Methoxybenzyl)pyrid-2-yl]-N'-2-(2-hydroxyethyl)-N''-phenylguanidine

A mixture of N-[6-(3-methoxybenzyl)pyrid-2-yl]-N'-phenylthiourea (1.0 g, 0.0029 mol), yellow mercuric oxide (0.74 g, 0.0034mol) and ethanolamine (0.52 g, 0.0086 mol) in methanol (40 ml) was stirred at room temperature for 2 days. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was washed with water, dried (K_2CO_3) and evaporated to an oil. Purification by column chromatography followed by treatment with ether-pet. ether gave the title compound as a crystalline solid. Yield 0.41 g (38%), m.p. 94-97 °C.

$C_{22}H_{24}N_4O_2$. 0.25 H_2O
Found C 69.04, H 6.38, N 14.49 Expected C 69.36, H 6.48, N 14.71

Example 44

N-[6-(4-Methoxybenzyl)pyrid-2-yl]-N'-methyl-N''-phenylguanidine maleate

A mixture of N-[6-(4-methoxybenzyl)pyrid-2-yl]-N'-phenylthourea (0.78 g, 0.002 mol), yellow mercuric oxide (0.58 g, 0.0026 mol) and methylamine (45 ml of 33% w/w solution in IMS) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue dissolved in a solution of maleic acid (0.25 g, 0.002 mol) in ethanol. The product crystallised on addition of ether.
Yield 0.42 g (55%), m.p. 136-138 °C.
$C_{21}H_{22}N_4O$.$C_4H_4O_4$
Found C 65.06, H 5.68, N 12.10 Expected C 64.92, H 5.67, N 12.11

Example 45

N-[6-(3-Methoxybenzyl)pyrid-2-yl]-N',N''-diphenylguanidine

A mixture of N-[6-(3-methoxybenzyl)pyrid-2-yl]-N'-phenylthourea (1 g, 0.0029 mol), yellow mercuric oxide (0.74 g, 0.0034 mol) and aniline (0.8 g, 0.0086 mol) was stirred for 2.5 days at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and purified by chromatography (ethyl acetate-dichloromethane) and crystallisation from ether - pet. ether.
Yield 0.2 g (17%), m.p. 109-111 °C.
$C_{26}H_{24}N_4O$. Found C 76.15, H 6.03, N 13.58 Expected C 76.45, H 5.92, N 13.72

Example 46

N-[2-(4-Methoxy)benzyl-3-methoxypyrid-6-yl]-N'-methyl-N''-phenylguanidine

A mixture of N-[6-(4-Methoxybenzyl)-5-methoxypyrid-2-yl]-N'-phenylthiourea (0.56 g, 0.0015 mol), yellow mercuric oxide (0.38 g, 0.0018 mol) and methylamine (15ml of a 33% w/w solution in ethanol) was stirred for 48 hours at room temperature. The solvent was removed *in vacuo* and the black residue was boiled with chloroform and filtered hot. The filtrate was evaporated and the residue crystallised from ether - pet. ether, then recrystallised from ethanol. Yield 0.22 g (40%), m.p. 80-82 °C.
$C_{22}H_{24}N_4O_2$. Found C 69.77, H 6.47, N 14.74 Expected C 70.19, H 6.43, N 14.74

Example 47.

N-(3-Benzylpyrid-2-yl)-N'-benzylguanidine hemimaleate

(a) **N-(3-Benzylpyrid-2-yl)-N'-benzylthiourea**

A mixture of 3-benzyl-2-aminopyridine (0.96 g, 0.0052 mol) and benzyl isothiocyanate (0.93 g, 0.0063 mol) in toluene (5 ml) was heated under reflux for 2.5 hr. The solvent was evaporated and the residue purified by flash chromatography (dichloromethane-pet. ether). Appropriate fractions were combined and evaporated to an oil, which crystallised on standing. Yield 0.74 g (43%), m.p. 110-12 °C.

(b) N-(3-Benzylpyrid-2-yl)-N'-benzylguanidine hemimaleate

To a stirring suspension of N-(3-benzylpyrid-2-yl)-N'-benzylthiourea (0.7 g, 0.0021 mol) in methanolic ammonia (20 ml) was added yellow mercuric oxide (0.55 g, 0.0025 mol). Stirring was continued for 2 days, then the solvent was evaporated and the black residue boiled with chloroform and filtered through celite. The filtrate was evaporated to an oil, which was dissolved in a solution of maleic acid (0.27 g) in ethanol. The product crystallised out on the addition of ether. Yield 0.4 g (51%), m.p. 116-118 °C.

$C_{20}H_{20}N_4 .0.5C_4H_4O_4$

Found C 70.41, H 5.99, N 14.99 Expected C 70.57, H 5.92, N 14.96

Example 48.

N-[3-Benzylpyrid-2-yl]-N'-(phenylamino)guanidine

(a) N-(3-Benzylpyrid-2-yl)-N-benzoylthiourea. An ice-cold solution of 3-benzyl-2-aminopyridine (4.7 g, 25.5 mmol) in benzene (40 ml) was treated with a solution of benzoylisothiocyanate (5.0 g, 30.6 mmol) in benzene (10 ml). Upon completion of the addition, the mixture was stirred at room temperature for 2h.

The solution was diluted with petroleum ether and ether and the resulting solid isolated. Yield 7.7 g (87%), m.p. 128-130 °C

(b) N-(3-Benzylpyrid-2-yl)thiourea.

Sodium hydroxide pellets (1.5 g, 37.5 mmol) were added to a stirred slurry of N-(3-benzylpyrid-2-yl)-N-benzoylthiourea (6.4 g, 18.4 mmol) in ethanol (20 ml) and water (30 ml). The mixture was refluxed for 1h, neutralised with acetic acid and finally basified with concentrated ammonium hydroxide solution. Upon ice cooling, the title compound crystallised and was isolated by filtration. Yield 4.3 g (96%), m.p. 176-179 °C.

(c) N-(3-Benzylpyrid-2-yl)-S-methylisothiourea

N-(3-Benzylpyrid-2-yl)thiourea (3.2 g, 13 mmol) and methyl iodide (46 g, 0.3 mol) were refluxed for 1h, then evaporated to dryness. The residue was dissolved in dichloromethane, washed with saturated aqueous sodium hydrogen carbonate solution, dried and evaporated to an oil which crystallised on standing. Yield 3.2 g (94%), m.p. 67-68 °C.

(d) N-[3-Benzylpyrid-2-yl]-N'-(phenylamino)guanidine

A solution of N-(3-benzylpyrid-2-yl)-S-methylisothiourea (1.5 g, 58 mmol) and phenylhydrazine (0.75 g, 70 mmol) in pyridine (20 ml) was refluxed for 24h, then evaporated to dryness. The residue was purified by flash chromatography (silica, 0 - 5%

methanol in dichloromethane). Evaporation of the appropriate fractions gave an oil which upon addition of petroleum ether gave orange crystals of the product.
Yield 0.32 g (17%), m.p. 80-81 °C.
$C_{19}H_{19}N_5$. Found C 72.30, H 5.55, N 22.18 Expected C 71.90, H 6.03, N 22.06

Example 49

N-[3-(2-Methylbenzyl)pyrid-2-yl]-N'-benzylguanidine maleate

(a) 2-Amino-3-(2-methylbenzyl)pyridine

A solution of 2-pivalamidopyridine (17.8 g, 0.1 mol) in dry THF (200 ml) at -78 °C was treated with a 2.5 M solution of n-butyllithium in hexane (100 ml, 0.25 mol). The solution was stirred at 0 °C for 3 hours, cooled to -10 °C and treated with 2-methylbenzaldehyde (18 g, 0.15 mol). After 1h at 0 °C, brine was added, the organic phase separated and the aqueous extracted with ether. The combined organic extracts were dried and evaporated to an oil which solidified upon the addition of petroleum ether. The carbinol was isolated and washed with ether (13.3 g, 44%). A portion of the above product (5.0 g, 16.7 mmol) was dissolved in pyridine (20 ml) and treated with acetic anhydride (20 ml) at 100 °C for 30 min. The mixture was evaporated to dryness and azeotroped twice with toluene. The residual oil, in methanol (30 ml), was hydrogenated at 50 psi in the presence of palladium hydroxide on carbon until hydrogen uptake ceased. The catalyst was removed by filtration, the filtrate evaporated to dryness and treated with 3N HCl (50 ml) under reflux for 3h. The cooled mixture was washed with ether, basified with aqueous sodium hydroxide and reextracted with ether. The organic extracts were dried and evaporated to give the title compound (3.0 g, 90%), m.p. 123-124 °C.

(b) N-[3-(2-Methylbenzyl)pyrid-2-yl]-N'-benzylthiourea

A mixture of 2-amino-3-(2-methylbenzyl)pyridine (1.5 g, 4.3 mmol) and benzyl isothiocyanate (1.3g, 5 mmol) in benzene (20 ml) was refluxed for 16h and evaporated to dryness. The residue was purified by flash chromatography using dichloromethane as the eluant. Evaporation of the appropriate fractions gave N-[3-(2-methylbenzyl)pyrid-2-yl]-N'-benzylthiourea (1.8 g, 67%), m.p. 126-128 °C.

(c) N-[3-(2-Methylbenzyl)pyrid-2-yl]-N'-benzylguanidine maleate

A mixture of N-[3-(2-methylbenzyl)pyrid-2-yl]-N'-benzylthiourea (1.5 g, 4.3 mmol) and yellow mercuric oxide (1.1 g, 5 mmol) in methanolic ammonia (20 ml) was stirred at room temperature for 48h then evaporated to dryness. The residue was triturated with dichloromethane, filtered and the filtrate evaporated. The resulting oil was treated with maleic acid (0.5 g, 4.3 mmol) in ethanol (5 ml) and diluted with ether. The precipitated solid was isolated and recrystallised from ethanol to give the title compound (1.1 g, 58%), m.p. 127-129 °C.

$C_{21}H_{22}N_4 .C_4H_4O_4$
Found C 67.02, H 5.90, N 12.58 Expected C 67.25, H 5.87, N 12.55

Example 50.

N-[3-{4-Methoxybenzyl}pyrid-2-yl]-N'-benzylguanidine maleate

(a) 2-Amino-3-(4-methoxybenzyl)pyridine

Substituting 4-methoxybenzaldehyde (20.4 g, 0.15 mol) for 2-methylbenzaldehyde and using corresponding molar proportions of the other reagents in Example 49A gave the intermediate carbinol (16.8 g, 53%). Using the procedure described in Example 49A but substituting 10% palladium on carbon for 5% palladium hydroxide on carbon, a portion of the carbinol (5.0 g, 16 mmol) was converted into the title compound (1.4 g, 42%), m.p. 126-128 °C.

(b) N-[3-{4-Methoxybenzyl}pyrid-2-yl]-N'-benzylthiourea

Substituing 2-amino-3-(4-methoxybenzyl)pyridine (1.4 g, 6.5 mmol) for 2-amino-3-(2-methylbenzyl)pyridine and using corresponding molar proportions of the other reagents in Example 49B gave N-[3-{4-methoxybenzyl}pyrid-2-yl]-N'-benzylthiourea (1.4 g, 59%), m.p. 85-86 °C.

(c) N-[3-{4-Methoxybenzyl}pyrid-2-yl]-N'-benzylguanidine maleate

Substituing N-[3-{4-methoxybenzyl}pyrid-2-yl]-N'-benzylthiourea (1.3 g, 3.6 mmol) for N-[3-(2-methylbenzyl)pyrid-2-yl]-N'-benzylthiourea and using corresponding molar proportions of the other reagents in Example 49C gave N-[3-{4-methoxybenzyl}pyrid-2-yl]-N'-benzylguanidine maleate (0.97g, 58%), m.p. 129-131 °C.

$C_{21}H_{22}N_4O .C_4H_4O_4$
Found C 64.91, H 5.74, N 12.25 Expected C 64.92, H 5.67, N 12.11

Example 51.

N-[3-(4-Methylbenzyl)pyrid-2-yl]-N'-(benzyl)guanidine

(a) 2-Amino-3-(4-methylbenzyl)pyridine

Substituting 4-methylbenzaldehyde (18.0 g, 0.15 mol) for 4-methoxybenzaldehyde and using corresponding molar proportions of the other reagents in Example 50A gave the intermediate carbinol (22.9 g, 77%). Using the procedure described in Example 50A, a portion of this material (5.0 g, 17 mmol) was converted into the title compound (2.6 g, 80%), m.p. 100-102 °C.

(b) N-[3-{4-Methylbenzyl}pyrid-2-yl]-N'-benzylthiourea

Substituting 2-amino-3-(4-methylbenzyl)pyridine (1.2 g, 6 mmol) for 2-amino-3-(2-methylbenzyl)pyridine and using corresponding molar proportions of the other reagents in Example 49B gave N-[3-{4-methylbenzyl}pyrid-2-yl]-N'-benzylthiourea (1.0 g, 48%), m.p. 100-102°C.

(c) N-[3-(4-Methylbenzyl)pyrid-2-yl]-N'-(benzyl)guanidine
Substituting N-[3-{4-methylbenzyl}pyrid-2-yl]-N'-benzylthiourea (1.0 g, 3 mmol) for N-[3-(2-methylbenzyl)pyrid-2-yl]-N'-benzylthiourea and using corresponding molar proportions of the other reagents in Example 49C gave N-[3-(4-methylbenzyl)pyrid-2-yl]-N'-(benzyl)guanidine (0.76 g, 59%), m.p. 126-128 °C.
$C_{21}H_{22}N_4 .C_4H_4O_4$
Found C 67.05, H 5.80, N 12.3 Expected C 67.25, H 5.87, N 12.55

Example 52.
N-[3-(4-Methoxybenzyl)pyrid-2-yl]-N'-(4-fluorobenzyl)guanidine maleate
(a) N-[3-{4-Methoxybenzyl}pyrid-2-yl]-N'-(4-fluorobenzyl)thiourea
Substituting 4-fluorobenzyl isothiocyanate (1.3 g, 8 mmol) for benzyl isothiocyanate and using corresponding molar proportions of the other reagents in Example 50B gave N-[3-{4-methoxybenzyl}pyrid-2-yl]-N'-(4-fluorobenzyl)thiourea (1.1 g, 42%), m.p. 93-94°C.
(b) N-[3-(4-Methoxybenzyl)pyrid-2-yl]-N'-(4-fluorobenzyl)guanidine maleate
Substututing N-[3-{4-methoxybenzyl}pyrid-2-yl]-N'-(4-fluorobenzyl)thiourea (1.0 g, 2.6 mmol) for N-[3-{4-methoxybenzyl}pyrid-2-yl]-N'-benzylthiourea and using corresponding molar proportions of the other reagents in Example 50C gave N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-(4-fluorobenzyl)guanidine maleate (0.66 g, 53%), m.p. 122-124 °C.
$C_{21}H_{21}FN_4O .C_4H_4O_4$
Found C 62.44, H 5.30, N 11.71 Expected C 62.49, H 5.24, N 11.66

Example 53.
N-[3-(Thien-2-ylmethyl)pyrid-2-yl]-N'-benzylguanidine maleate
(a) 2-Pivalamido-3-(thien-2-ylhydroxymethyl)pyridine
A solution of 2-pivalamidopyridine (17.8 g, 0.1 mol.) in dry tetrahydrofuran (200 ml) was stirred at -70 °C in an atmosphere of nitrogen and treated with n-butyllithium (100 ml of a 2.5M solution in hexane). The mixture was warmed to 0 °C and stirred for 3 hours, then recooled to -30°C and a solution of thiophenecarboxaldehyde (16.8 g, 0.15mol) in dry tetrahydrofuran (50 ml) added dropwise. The mixture was allowed to warm to room temperature, stirred for 1 hour, then poured onto ice and extracted twice with ether. The combined extracts were washed with water and brine, dried and evaporated to an oil which crystallised on standing. The product was triturated with pet. ether to give the title compound (14.0 g, 48%), m.p. 156-158 °C.
(b) 2-Amino-3-(thien-2-ylmethyl)pyridine
Sodium borohydride pellets (5.2 g, 0.137 mol) were added, one at a time, to trifluoroacetic acid (250 ml) under a slow stream of nitrogen. 2-Pivalamido-3-(thien-2-

ylhydroxymethyl)pyridine was then added and the mixture stirred at room temperature for 3 hours. The tifluoroacetic acid was evaporated and the residue was heated under reflux in 5M HCl for 1 h. The mixture was cooled, neutralised with ammonium carbonate and extracted twice with chloroform. The combined extracts were dried, filtered and evaporated to an oil. Chromatography (silica gel, chloroform, 0 - 1% methanol) gave 2-pivalamido-3-(thien-2-ylmethyl)pyridine (4 g). The required 2-amino-3-(thien-2-ylmethyl)pyridine was obtained by heating the pivalamide under reflux again in 5M HCl. Yield 2.5 g (38%), m.p. 100-101 °C.

(c) N-[3-(Thien-2-ylmethyl)pyrid-2-yl]-N'-benzylthiourea

A mixture of 2-amino-3-(thien-2-ylmethyl)pyridine (1.24 g, 38 mmol) and benzyl isothiocyanate (0.75 g, 50 mmol) was heated under reflux in toluene (50 ml) for 6 h, an additional amount of benzyl isothiocyanate (1 ml) being added after 3 h. The mixture was evaporated and chromatographed (silica gel, chloroform) to give the title compound as an oil (1 g, 77%).

(d) N-[3-(Thien-2-ylmethyl)pyrid-2-yl]-N'-benzylguanidine maleate

A mixture of N-[3-(thien-2-ylmethyl)pyrid-2-yl]-N'-benzylthiourea (1.0 g, 29 mmol) and mercuric oxide (0.74 g, 34 mmol) was stirred in methanolic ammonia (30 ml) for 24 h, then filtered through celite and evaporated to give a residue which was taken up in ethanol containing maleic acid (0.34 g, 29 mmol). Addition of ether produced a solid which was recrystallised from ethyl acetate. Yield 0.5 g (39%), m.p. 110-112 °C.

$C_{18}H_{18}N_4S \cdot C_4H_4O_4 \cdot 0.25EtOAc$

Found C 59.67, H 5.05, N 12.57 Expected C 59.98, H 5.05, N 12.17

Example 54.

N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-4-cyanobenzylguanidine maleate

(a) 2-Pivalamido-3-(4-methoxy-α-hydroxybenzyl)pyridine

A solution of 2-pivalamidopyridine (17.8 g, 0.1 mol) in dry THF (200 ml) at -78 °C was treated with a 2.5 M solution of n-butyllithium in hexane (100 ml, 0.25 mol). The solution was stirred at 0 °C for 3h, cooled to -10 °C and treated with 2-methylbenzaldehyde (18 g, 0.15 mol). After 1 hour at 0 °C, brine was added, the organic phase separated and the aqueous extracted with ether. The combined organic extracts were dried and evaporated to an oil which solidified upon the addition of petroleum ether. Yield 13.3 g (44%).

(b) 2-Amino-3-(4-methoxybenzyl)pyridine

Sodium borohydride pellets (4.8 g, 0.127 mol) were added, one at a time, to trifluoroacetic acid (200 ml) under a slow stream of nitrogen. 2-Pivalamido-3-(4-methoxy-α-hydroxybenzyl)pyridine (10 g, 0.032 mol) was added and the mixture stirred for 3 h. The solvent was evaporated and the residue was heated in 5M HCl over a steam bath for 1 h. The mixture was cooled, neutralized with ammonium carbonate and extracted twice with

chloroform. The combined extracts were dried, filtered and evaporated. Chromatography (silica gel, 0-2% methanol in chlorofom) gave the title compound (2.5 g, 36.5%), m.p. 125-126 °C.

(c) 4-Cyanobenzyl isothiocyanate

A mixture of 4-cyanobenzylamine (1.58 g, 0.012 mol) and di-2-pyridoxythione (2.8 g, 0.012 mol) were stirred together in acetonitrile (50 ml) for 2 h. The solvent was evaporated and the residue was dissolved in dichloromethane, washed twice with water and 2M HCl. The organic solution was dried, filtered and evaporated to give the title compound as a brown oil (1.6 g, 77%).

(d) N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-4-cyanobenzyl thiourea

A mixture of 4-cyanobenzyl isothiocyanate (1.4 g, 0.008 mol) and 2-amino-3-(4-methoxy-benzyl)pyridine (1.3g, 0.0061mol) was heated under reflux in toluene (50 ml) for 18 h. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, chloroform - pet. ether 1:1 - 2:1) to give the title compound as a yellow gum (1.54 g, 65%).

(e) N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-4-cyanobenzylguanidine maleate

A mixture of N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-4-cyanobenzylthiourea (1.5 g, 0.0039 mol) and mercuric oxide (0.92 g, 0.00425 mol) in methanolic ammonia (30 ml) was stirred at room temperature for 3 days. The mixture was filtered through celite, evaporated, dissolved in ethanol and refiltered. Maleic acid (0.45 g, 0.0038 mol) was added, the solution was reduced in volume, and ether added to induce crystallisation of the title compound, which was recrystallised from ethanol. Yield 1.3 g (69%), m.p. 73-74 °C.

$C_{22}H_{21}N_5O .C_4H_4O_4 .0.5H_2O$

Found C 62.87 H 5.16 N 14.15 Expected C 62.89 H5.28 N 14.11

Example 55.

N-(3-(1-(4-Methoxyphenyl)ethyl)pyrid-2-yl)-N'-benzylguanidine maleate

(a) 2-Pivalamido-3-[1-(4-methoxyphenyl)hydroxyethyl]pyridine

A solution of n-butyllithium (2.5M in hexane, 100 ml) was added dropwise to a stirred solution of 2-pivalamidopyridine (17.8 g, 0.1 mol) in dry tetrahydrofuran (200 ml) at -70 °C under an atmosphere of nitrogen. The mixture was allowed to warm to 0 °C and stirred for 3h. The mixture was re-cooled to -30 °C and a solution of 4-methoxy-acetophenone (22.5 g, 0.15 mol) in dry tetrahydrofuran (50 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was poured onto a mixture of ice water and ether, the layers separated and the aqeous was extracted with ether. The combined ether solutions were washed with water and brine, dried, filtered and evaporated to a crystalline solid which was slurried in ether and filtered off to give the title compound (32.8 g, 37%), m.p. 208-210 °C.

(b) 2-Amino-3-[1-(4-methoxyphenyl)ethenyl]pyridine and 2-amino-3-[1-(4-hydroxyphenyl)ethenyl]pyridine

Sodium borohydride pellets (6.0 g, 0.16 mol) were added, one at a time, to trifluoroacetic acid (200 ml) cooled in an ice bath under a slow stream of nitrogen. 2-Pivalamido-3-[1-(4-methoxyphenyl)hydroxyethyl]pyridine (12 g, 0.036 mol) was added and the mixture stirred at room temperature for 2h. The solvent was evaporated and the residue was diluted with water, basified (Na_2CO_3),and extracted twice with ethyl acetate. The combined extracts were dried, filtered and evaporated. The residue was taken up in 5M HCl and heated under reflux for 24 hours. Slurrying with ether and filtration gave 2-amino-3-[1-(4-methoxy-phenyl)ethenyl]pyridine (5.2 g, 64%), m.p.154-155 °C.

The ethereal filtrate was evaporated, taken up in 5M HCl and heated under reflux for a further 24 h. The acidic solution was basified (Na_2CO_3) and extracted twice with ethyl acetate. The combined extracts were washed with brine, dried, filtered and evaporated to a solid which was slurried in ether, filtered off and dried to give 2-amino-3-[1-(4-hydroxyphenyl)ethenyl]pyridine (1.32 g, 17.3%), m.p. 177-179 °C.

(c) 2-Amino-3-(1-(4-methoxyphenyl)ethyl)pyridine

A mixture of 2-amino-3-[1-(4-methoxyphenyl)ethenyl]pyridine (5.1 g, 0.0225 mol) and 10% palladium on carbon (0.5 g) in ethanol (100 ml) was shaken under hydrogen (40 p.s.i) for 6 h. The mixture was filtered through celite and evaporated to give the title compound (5.0 g, 98%), m.p. 138-140 °C.

(d) N-(3-(1-(4-Methoxyphenyl)ethyl)pyridyl)-N'-benzylthiourea

A mixture of 2-amino-3-[1-(4-methoxylphenyl)ethyl]pyridine (1.7 g, 0.0075 mol) and benzyl isothiocyanate (2.25 g, 0.015 mol) in toluene (25 ml) was heated under reflux for 2 h. The solvent was evaporated and the residual yellow oil was chromatographed (silica, chloroform -pet. ether 1:1) to give the title compound as a yellow oil which crystallised on standing. Yield 1.5 g (53%), m.p. 140-142 °C.

(e) N-(3-(1-(4-Methoxyphenyl)ethyl)pyrid-2-yl)-N'-benzylguanidine maleate

A mixture of N-[3-[1-(4-methoxyphenyl)ethyl]pyrid-2-yl]-N'-benzylthiourea (1.2 g, 0.003 mol) and mercuric oxide (0.76 g, 0.0033 mol) were stirred together in methanolic ammonia (75 ml) for 3 days. The mixture was filtered through celite, evaporated, dissolved in ether and filtered through paper to remove residual solids. A solution of maleic acid (0.35 g, 0.003 mol) in ethanol (3 ml) was added and the mixture was stored in a freezer for several days. The crystalline product was isolated and recrystallised from ether to give the title compound (1.1 g, 77%), m.p. 95-96 °C

$C_{22}H_{24}N_4O \cdot C_4H_4O_4 \cdot 0.3H_2O$

Found C 64.74, H 5.92, N 11.63 Expected C 64.80, H 5.98, N 11.63

Example 56.

N-[3-Benzylpyrid-2-yl]-N'-(2-chlorobenzyl)guanidine maleate

(a) N-[3-Benzylpyrid-2-yl]-N'-(2-chlorobenzyl)thiourea

Substituting 2-chlorobenzyl isothiocyanate (2.4 g, 13 mmol) for benzyl isothiocyanate and using corresponding molar proportions of the other reagents in Example 1A gave N-[3-benzylpyrid-2-yl]-N'-(2-chlorobenzyl)thiourea (2.4 g, 60%), m.p. 139-140 °C.

(b) N-[3-Benzylpyrid-2-yl]-N'-(2-chlorobenzyl)guanidine maleate

Substituting N-[3-benzylpyrid-2-yl]-N'-(2-chlorobenzyl)thiourea (1.2 g, 3.3 mmol) for N-(3-benzylpyrid-2-yl)-N'-benzylthiourea and using corresponding molar proportions of the other reagents in Example 1B gave N-[3-benzylpyrid-2-yl]-N'-(2-chlorobenzyl)guanidine maleate (0.9 g, 59%), m.p. 146-148 °C.

$C_{20}H_{19}ClN_4 .C_4H_4O_4$

Found C 61.76, H 4.99, N 11.68, Cl 7.73 Expected C 61.74, H 4.97, N 12.00, Cl 7.59

Example 57.

N-(3-Benzylpyrid-2-yl)-N'-(4-chlorobenzyl)guanidine hemimaleate

(a) N-(3-Benzylpyrid-2-yl)-N'-(4-chlorobenzyl)thiourea

Substituting 4-chlorobenzyl isothiocyanate (1.7 g, 9.3 mmol) for benzyl isothiocyanate and using corresponding molar proportions of the other reagents in Example 47A gave N-(3-benzylpyrid-2-yl)-N'-(4-chlorobenzyl)thiourea (2.1 g, 57%), m.p. 107.5-108.5 °C.

(b) N-(3-Benzylpyrid-2-yl)-N'-(4-chlorobenzyl)guanidine hemimaleate

Substituting N-(3-benzylpyrid-2-yl)-N'-(4-chlorobenzyl)thiourea (1.0 g, 2.7 mmol) for N-(3-benzylpyrid-2-yl)-N'-benzylthiourea and using corresponding molar proportions of the other reagents in Example 47B gave N-(3-benzylpyrid-2-yl)-N'-(4-chlorobenzyl)guanidine hemimaleate (0.6 g, 55%), m.p. 164-166 °C.

$C_{20}H_{19}ClN_4 .0.45C_4H_4O_4$

Found C 64.66, H 5.32, N 13.67 Expected C 64.62, H 5.18, N 13.70

Example 58

N-(3-Benzylpyrid-2-yl)-N'-(4-methylbenzyl)guanidine

(a) N-(3-Benzylpyrid-2-yl)-N'-(4-methylbenzyl)thiourea

Substituting 4-methylbenzyl isothiocyanate (2.0 g, 12 mmol) for benzyl isothiocyanate and using corresponding molar proportions of the other reagents in Example 47A gave N-(3-benzylpyrid-2-yl)-N'-(4-methylbenzyl)thiourea (2.05 g, 55%), m.p. 124-125 °C.

(b) N-(3-Benzylpyrid-2-yl)-N'-(4-methylbenzyl)guanidine

Substituting N-(3-benzylpyrid-2-yl)-N'-(4-methylbenzyl)thiourea (1.5 g, 4.3 mmol) for N-(3-benzylpyrid-2-yl)-N'-benzylthiourea and using corresponding molar proportions of the

other reagents in Example 47B gave N-(3-benzylpyrid-2-yl)-N'-(4-methylbenzyl)guanidine (0.81 g, 42%), m.p. 104-106 °C.

$C_{20}H_{19}ClN_4 .C_4H_4O_4$

Found C 67.17, H 5.96, N 12.66 Expected C 67.25, H 5.87, N 12.55

Example 59.

N-[3-Benzylpyrid-2-yl]-N'-(4-methoxybenzyl)guanidine maleate

(a) N-[3-Benzylpyrid-2-yl]-N'-(4-methoxybenzyl)thiourea

Substituting 4-methoxybenzyl isothiocyanate (2.3 g, 13 mmol) for benzyl isothiocyanate and using corresponding molar proportions of the other reagents in Example 47A gave N-[3-benzylpyrid-2-yl]-N'-(4-methoxybenzyl)thiourea (2.6 g, 66%), m.p. 99.5-100.5 °C.

(b) N-[3-Benzylpyrid-2-yl]-N'-(4-methoxybenzyl)guanidine maleate

Substituting N-[3-benzylpyrid-2-yl]-N'-(4-methoxybenzyl)thiourea (1.9 g, 5.0 mmol) for N-(3-benzylpyrid-2-yl)-N'-benzylthiourea and using corresponding molar proportions of the other reagents in Example 47B gave N-[3-benzylpyrid-2-yl]-N'-(4-methoxybenzyl)guanidine maleate (1.7 g, 74%), m.p. 130-132 °C.

$C_{21}H_{22}N_4O .C_4H_4O_4$

Found C 64.92, H 5.71, N 12.24 Expected C 64.92, H 5.67, N 12.11

Example 60.

N-(3-Benzylpyrid-2-yl)-N'-benzyl-N"-hydroxyguanidine

(a) N-(3-Benzylpyrid-2-yl)-N'-benzyl-S-methylisothiourea

Methyl iodide (20 ml) and N-(3-benzylpyrid-2-yl)-N'-benzylthiourea (3.0 g, 9 mmol) were refluxed for 1h and evaporated to dryness. The residue was dissolved in dichloromethane, washed with sodium hydrogen carbonate solution, dried and evaporated to a yellow solid (3.1 g, 99%), m.p. 104-105.5 °C.

(b) N-(3-Benzylpyrid-2-yl)-N'-benzyl-N"-hydroxyguanidine

To a solution of sodium (70 mg, 3 mmol) in ethanol (20 ml) was added hydroxylamine hydrochloride (0.21 g, 3 mmol). The mixture was heated and N-(3-benzylpyrid-2-yl)-N'-benzyl-S-methylisothiourea (0.95 g, 27 mmol) was added. The mixture was refluxed for 16h, cooled and evaporated to dryness. The residual oil, in dichloromethane, was washed with water, brine, dried and evaporated. The residue was purified by flash chromatography (silica, 2% methanol in dichloromethane). Evaporation of the appropriate fractions gave an oil which solidified when treated with petroleum ether. Recrystallisation from ethyl acetate gave N-(3-benzylpyrid-2-yl)-N'-benzyl-N"-hydroxyguanidine (0.1 g, 11%), m.p. 149-151°C.

$C_{20}H_{20}N_4O$. Found C 72.38, H 6.16, N 16.75 Expected C 72.27, H 6.06, N 16.85

Example 61.

N-[3-Benzylpyrid-2-yl]-N'-benzyl-N''-methoxyguanidine

A solution of N-(3-benzylpyrid-2-yl)-N'-benzyl-S-methylisothiourea (2.0 g, 6 mmol) and methoxylamine hydrochloride (0.5 g, 6 mmol) in pyridine (10 ml) was heated at 85 °C for 4h. The reaction was evaporated to dryness and the residue purified by flash chromatography (silica, 0 - 10% ethyl acetate in hexane). Evaporation of the appropriate fractions gave an oil which solidified upon the addition of petroleum ether. Yield 0.2 g (10%), m.p. 70-71 °C.

$C_{21}H_{22}N_4O$. Found C 72.63, H 6.46, N 16.24 Expected C 72.81, H 6.40, N 16.17

Example 62.

N-(3-Benzylpyrid-2-yl)-N'-phenylguanidine maleate

(a) N-(3-Benzylpyrid-2-yl)-N'-phenylthiourea

Substituting phenyl isothiocyanate (1.5 g, 11 mmol) for benzyl isothiocyanate and using corresponding molar proportions of the other reagents in Example 47A gave N-(3-benzylpyrid-2-yl)-N'-phenylthiourea (2.6 g, 81%), m.p. 134-136 °C.

(b) N-(3-Benzylpyrid-2-yl)-N'-phenylguanidine maleate

Substituting N-(3-benzylpyrid-2-yl)-N'-phenylthiourea (1.6 g, 5.0 mmol) for N-(3-benzylpyrid-2-yl)-N'-benzylthiourea and using corresponding molar proportions of the other reagents in Example 47B gave N-(3-benzylpyrid-2-yl)-N'-phenylguanidine maleate (1.7 g, 82%), m.p. 132-134 °C.

$C_{19}H_{18}N_4 .C_4H_4O_4 .0.1H_2O$

Found C 65.51, H 5.32, N 13.38 Expected C 65.73, H 5.28, N 13.33

Example 63.

N-[3-Thien-2-ylmethyl)pyrid-2-yl]-N'-phenylguanidine maleate

(a) N-[3-(Thien-2-ylmethyl)pyrid-2-yl]-N'-phenylthiourea

A mixture of 2-amino-3-(thien-2-ylmethyl)pyridine (1.2 g, 63 mmol) and phenyliso-thiocyanate (1.13 g, 83 mmol) were heated together under reflux in toluene (30 ml) for 4 h. The solvent was evaporated and the residue was triturated with ether-pet. ether to give the title compound (1.1 g, 54%), m.p. 126-128 °C.

(b) N-[3-(Thien-2-ylmethyl)pyrid-2-yl]-N'-phenylguanidine maleate

A mixture of N-[3-(thien-2-ylmethyl)pyrid-2-yl]-N'-phenylthiourea (1.0 g, 0.003 mol) and mercuric oxide (0.745 g, 0.00344 mol) was stirred in methanolic ammonia (30 ml) for 3 days, then filtered through celite and evaporated to an oil. The residue was dissolved in ethanol and maleic acid (0.35 g, 0.003 mol) in ethanol was added. The solvent was evaporated and the residue chromatographed (silica, 0-2% methanol in chloroform) and crystallised from ether. Yield 0.62 g (49%), m.p. 143-144 °C.

$C_{17}H_{16}N_4S$.$C_4H_4O_4$
Found C 59.26, H 4.86, N 13.19 Expected C 59.42, H 4.75, N 13.20

Example 64.

N-[3-(4-Hydroxybenzyl)pyrid-2-yl]-N'-phenylguanidine

(a) 2-Amino-3-(4-hydroxybenzyl)pyridine

A solution of 2-amino-3-(4-methoxybenzyl)pyridine (4.3 g, 0.02 mol), under nitrogen, was cooled to 0 °C and treated with boron tribromide (15.9 g, 0.063 mol). The mixture was allowed to warm to room temperature where it solidified to a gel. After 1h the mixture was poured onto ice, neutralised with sodium carbonate and extracted twice with chloroform. The combined extracts were washed with water, dried, filtered and evaporated to a yellow solid (3.0 g, 75%), m.p. 153-155 °C.

(b) N-[3-(4-Hydroxybenzyl)pyrid-2-yl]-N'-phenylthiourea

A mixture of 2-amino-3-(4-hydroxybenzyl)pyridine (3.0 g, 0.015 mol) and phenylisothiocyanate (3.4 g, 0.025 mol) in toluene (100 ml) was heated under reflux for 4 h. The solvent was evaporated and the residue chromatographed (silica gel, 0-1% methanol in chloroform). Yield 2.3 g (46%), m.p. 178-180 °C.

(c) N-[3-(4-Hydroxybenzyl)pyrid-2-yl]-N'-phenylguanidine

A mixture of N-[3-(4-Hydroxybenzyl)pyrid-2-yl]-N'-phenylthiourea (1.74 g, 0.005 mol) and mercuric oxide (1.2 g, 0.055 mol) were stirred together in methanolic ammonia (100 ml) for 24 h. The mixture was filtered through celite, evaporated, dissolved in ethanol-ether and refiltered. The filtrate was evaporated and crystallised from ether to give the title compound (0.8 g, 50%), m.p.189-190 °C.
$C_{19}H_{18}N_4O$. Found C 71.38, H 5.83, N 17.54 Expects C 71.68, H 5.70, N 17.60

Example 65.

N-[3-(4-Methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine

(a) N-[3-(4-Methoxybenzyl)pyrid-2-yl]-N'-phenylthiourea

A mixture of 2-amino-3-(4-methoxybenzyl)pyridine (0.745 g, 0.0035 mol) and phenyliso-thiocyanate (0.68 g, 0.005 mol) in toluene (20 ml) was heated under reflux for 3.5 h. The solvent was evaporated and the title compound crystallised from ether. Yield 0.8 g (65.5%), m.p. 103-105 °C.

(b) N-[3-(4-Methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine

A mixture of N-[3-(4-Methoxybenzyl)pyrid-2-yl]-N'-phenylthiourea (0.73 g, 0.002 mol) and mercuric oxide (0.477 g, 0.0022 mol) were stirred together in methanolic ammonia (20 ml) for 48 h. The mixture was filtered through celite and evaporated to an oil which was taken up in ether. Maleic acid (0.23 g, 0.002 mol) in ethanol was added, the solvent

was evaporated, and the residue chromatographed (silica, 0-2% methanol in chloroform) and crystallised from ether. Yield 0.43 g (48%), m.p. 165-166 °C.

$C_{20}H_{20}N_4O .C_4H_4O_4$

Found C 64.21, H 5.60, N12.22 Expects C 64.28, H 5.39, N 12.49

Example 66.

N-(3-Benzylpyrid-2-yl)-N'-(4-chlorophenyl)guanidine maleate

(a) N-(3-Benzylpyrid-2-yl)-N'-(4-chlorophenyl)thiourea

Substituting 4-chlorophenyl isothiocyanate (1.7 g, 10 mmol) for benzyl isothiocyanate and using corresponding molar proportions of the other reagents in Example 47A gave N-(3-benzylpyrid-2-yl)-N'-(4-chlorophenyl)thiourea (1.7 g, 55%), m.p. 140-141°C.

(b) N-(3-Benzylpyrid-2-yl)-N'-(4-chlorophenyl)guanidine maleate

Substituting N-[3-benzylpyrid-2-yl]-N'-(4-chlorophenyl)thiourea (1.2 g, 3.3 mmol) for N-(3-benzylpyrid-2-yl)-N'-benzylthiourea and using corresponding molar proportions of the other reagents in Example 47B gave N-(3-benzylpyrid-2-yl)-N'-(4-chlorophenyl)guanidine (0.7 g, 30%), m.p. 114-116 °C.

$C_{19}H_{17}ClN_4O .C_4H_4O_4$

Found C 60.63, H 4.75, N 12.15, Cl 8.02 Expected C 61.00, H 4.67, N 12.37, Cl 7.83

Example 67.

N-3-(4-Hydroxyphenyleth-2-yl)pyrid-2-yl-N'-phenylguanidine maleate

(a) 2-Amino-3-[1-(4-hydroxyphenyl)ethyl]pyridine

A mixture of 2-amino-3-[1-(4-hydroxyphenyl)ethenyl]pyridine (1.32 g, 0.0062 mol) and 10% palladium on carbon (0.2 g) in ethanol (100 ml) was shaken under hydrogen (40 p.s.i) at room temperature for 8 hours, then at 50 °C for 4h. The mixture was filtered through celite and evaporated to give the title compound (1.2 g, 90%), m.p. 163-165 °C.

(b) N-3-[1-(4-Hydroxyphenyl)ethyl]pyrid-2-yl-N'-phenylthiourea

A mixture of 2-amino-3-[1-(4-hydroxylphenyl)ethyl]pyridine (1.2 g, 0.0056 mol) and phenylisothiocyanate (2.26 g, 0.017 mol) in toluene (75 ml) was heated under reflux for 3h. The solvent was evaporated and the residue was chromatographed (silica, chloroform -pet. ether 1:1 - 1% methanol in chloroform) to give the title compound as an oil (0.75 g, 38%).

(c) N-3-(4-Hydroxyphenyleth-2-yl)pyrid-2-yl-N'-phenylguanidine maleate

A mixture of N-3-[1-(4-Hydroxyphenyl)ethyl]pyrid-2-yl-N'-phenylthiourea (0.72 g, 0.002 mol) and mercuric oxide (0.49 g, 0.0022 mol) was stirred together in methanolic ammonia (50 ml) for 3 days. The mixture was filtered through celite and evaporated to an oil which was dissolved in ether and refiltered. Maleic acid (0.23 g, 0.002 mol) in ethanol was added, the mixture refrigerated for 2 days, and the salt filtered off and recrystallised from ethanol. Yield 0.68 g (76%), m.p. 173-174 °C.

$C_{20}H_{20}N_4O$.$C_4H_4O_4$ .0.15EtOAc
Found C 63.72, H 5.46, N 12.38 Expects C 64.00, H 5.50, N 12.14

Example 68.

N-[3-{1-(4-Methoxyphenyl)ethyl}pyrid-2-yl]-N'-phenylguanidine maleate

N-3-[1-(4-Methoxyphenyl)ethyl]pyrid-2-yl-N'-phenylthiourea

A mixture of 2-amino-3-[1-(4-methoxyphenyl)ethyl]pyridine (1.7 g, 0.0075 mol) and phenyl isothiocyanate (2.26 g, 0.017 mol) in toluene (100 ml) was heated under reflux for 2 h. The solvent was evaporated and the residue was chromatographed (silica, chloroform-hexane 1:1 - chloroform) to give the title compound as an oil (2.1 g, 78%).

(c) N-[3-{1-(4-Methoxyphenyl)ethyl}pyrid-2-yl]-N'-phenylguanidine maleate

A mixture of N-3-[1-(4-methoxyphenyl)ethyl]pyrid-2-yl-N'-phenylthiourea (2.0 g, 0.0055 mol) and mercuric oxide (1.31 g, 0.006 mol) in methanolic ammonia (75 ml) was stirred overnight and filtered through celite. Evaporation gave a clear oil which was dissolved in ether and refiltered. A solution of maleic acid (0.6 g, 0.005 mol) in ethanol was added and the mixture stored in the freezer for 48 h. The crystalline product was isolated and recrystallised from ethanol-ether. Yield 1.58 g (62%), m.p. 125-126 °C.

$C_{21}H_{22}N_4O$.$C_4H_4O_4$
Found C 65.30, H 5.72, N 12.19 Expects C 64.92, H 5.67, N 12.11

Example 69.

N-[3-Benzylpyrid-2-yl]-N'-phenyl-N''-dimethylguanidine

Substituting dimethylamine in methanol for ammonia in methanol and using corresponding molar proportions of the other reagents in Example 62B gave N-[3-benzylpyrid-2-yl]-N'-phenyl-N''-dimethylguanidine (0.7 g, 71%), m.p. 68-70 °C.

$C_{21}H_{22}N_4$. Found C 76.21, H 6.77, N 17.14 Expected C 76.33, H 6.71, N 16.96

Biological Data.

H^+K^+ATPase Activity

The effects of a single high concentration (100 mM) of a compound of structure (I) on K-stimulated ATPase activity in lyophilised gastric vesicles was determined. Preferred compounds of structure (I) were also tested over a range of concentrations to determine IC_{50} values.

(i) **Preparation of lyophilised gastric vesicles (H/K-ATPase)**

Lyophilised gastric vesicles were prepared from pig fundic mucosa after the method of Keeling et. al. (Biochem. Pharmacol., 34, 2967, 1985).

(ii) **K^+-stimulated ATPase activity**

K^+-stimulated ATPase activity was determined at 37°C in the presence of the following : 10 mM Pipes/Tris buffer pH 7.0, 2 mM $MgSO_4$, 1 mM KCl, 2 mM Na_2ATP and 3-6 mg protein/ml lyophilised gastric vesicles. After incubation for 30 minutes, the inorganic phosphate hydrolysed from ATP was determined by the method of Yoda and Hokin (Biochem. Biophys. Res. Commun. 40, 880, 1970).

Compounds of structure (I) were dissolved in dimethylsulphoxide which up to the highest concentration used had no effect on K^+-stimulated ATPase activity.

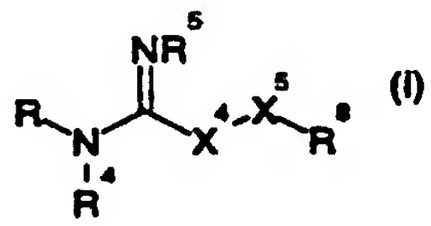
The effect of the highest concentration of each compound of structure (I) on the recovery of a standard amount of inorganic phosphate was also determined.

Results

The compounds of the examples exhibited IC_{50} values of less than 55 m M.

Claims:

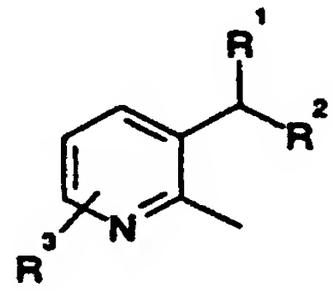
1. A compound of structure (I) or a salt thereof:



(I)

in which:

R is a group of formula (i):



(i)

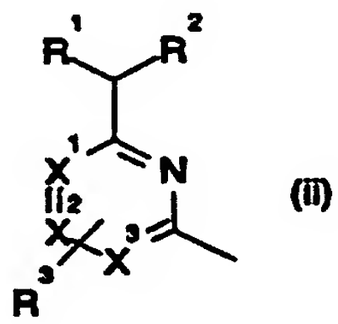
in which:

R^1 is an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 is hydrogen or C_{1-6}alkyl;

R^3 is hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

or R is a group of formula (ii):



(ii)

in which R^1, R^2 and R^3 are as defined in formula (i) above and

X^1, X^2 and X^3 are all CH groups or one of X^1, X^2 or X^3 is nitrogen and the others are CH groups;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxy or phenyl;

X^4 is CH_2 or NR^6 where R^6 is hydrogen or C_{1-6}alkyl;

X^5 is a single bond, CH_2 or NR^7 where R^7 is hydrogen or C_{1-6}alkyl; and

R^8 is C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkylC_{3-6}cycloalkyl, C_{1-6}alkoxyC_{1-6}alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6- membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen or sulphur.

2. A compound according to claim 1 in which R is a group of formula (i).

3. A compound according to claim 1 in which R is a group of formula (ii).

4. A compound according to claim 3 in which X^1, X^2 and X^3 are all CH groups.

5. A compound according to any one of claims 1 to 4 in which R^2 and R^3 are both hydrogen.

6. A compound according to any one of claims 1 to 5 in which R^1 is thienyl, phenyl or phenyl substituted by C_{1-6}alkyl, C_{1-6}alkoxy, halogen, amino or nitro.

7. A compound according to claim 1 which is

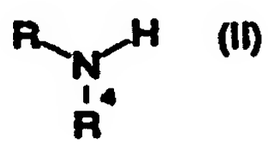
N-(6-benzyl-2-pyridyl)phenylacetamidine,
N-[6-(2-methylbenzyl)pyrid-2-yl]phenylacetamidine,
N-(2-benzyl-4-pyrimidinyl)-N'-phenylguanidine,
N-[4-(N-methylphenylamino)-2-pyrimidyl]-N'-(4-chlorophenyl)-guanidine,
N-[4-(N-methylphenylamino)-2-pyrimidyl]-N'-phenylguanidine,
N-[2-(N-methylphenylamino)-4-pyrimidyl]-N'-(4-chlorophenyl)-guanidine,
N-(4-benzyl-2-pyrimidinyl)-N'-(4-chlorophenyl)guanidine,
N-(4-benzyl-2-pyrimidinyl)-N'-phenylguanidine,
N-(6-benzylpyrazin-2-yl)-N'-phenylguanidine,
N-[6-(2-methylphenylmethyl)]pyrid-2-yl-N'-(4-chlorophenyl)-guanidine,
N-[6-(2-methylphenylmethyl)pyrid-2-yl]-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-(4-chlorophenyl)guanidine,
N-[6-(4-methylbenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-[6-(4-methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-(2-methylphenyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(2-chlorophenyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(3-methoxyphenyl)guanidine,
N-[6-(3-methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine,

N-(6-benzylpyrid-2-yl)-N'-(3-chlorophenyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(4-methoxyphenyl)guanidine,
N-(2-benzyl-3-methoxypyrid-6-yl)-N'-phenylguanidine,
N-[6-(4-fluorobenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-[6-(4-nitrobenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-[6-(4-aminophenylmethyl)pyrid-2-yl]-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-(4-cyanophenyl)guanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(4-methylthiophenyl)guanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(4-methylsulphonylphenyl)-guanidine,
N-[6-(4-methoxybenzyl)-5-methoxypyrid-2-yl]-N'-phenylguanidine,
N-[6-(4-methoxybenzyl)pyrid-2-yl]-N'-methylguanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(2-pyrimidyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-benzylguanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(2-thiazolyl)guanidine,
N-[6-(benzylpyrid-2-yl)]-N'-(2-pyrazinyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(5-pyrimidyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-(3-methoxypropyl)guanidine,
N-(6-benzylpyrid-2-yl)-N'-cyclohexylguanidine,
N-(6-benzylpyrid-2-yl)-N'-(2-methoxyethyl)guanidine,
N-[(6-benzyl)pyrid-2-yl]-N'-butylguanidine,
N-(6-benzylpyrid-2-yl)-N'-methyl-N'-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N'-methyl-N''-phenylguanidine,
N-(6-benzylpyrid-2-yl)-N',N'-dimethyl-N''-phenylguanidine,
N-[6-(3-methoxybenzyl)pyrid-2-yl]-N'-2-(2-hydroxyethyl)-N''-phenylguanidine,
N-[6-(4-methoxybenzyl)pyrid-2-yl]-N'-methyl-N''-phenyl-guanidine,
N-[6-(3-methoxybenzyl)pyrid-2-yl]-N',N''-diphenylguanidine,
N-[2-(4-methoxy)benzyl-3-methoxypyrid-6-yl]-N'-methyl-N''-phenylguanidine,
N-(3-benzylpyrid-2-yl)-N'-benzylguanidine,
N-[3-benzylpyrid-2-yl]-N'-(phenylamino)guanidine,
N-[3-(2-methylbenzyl)pyrid-2-yl]-N'-benzylguanidine,
N-[3-{4-methoxybenzyl}pyrid-2-yl]-N'-benzylguanidine,
N-[3-(4-methylbenzyl)pyrid-2-yl]-N'-(benzyl)guanidine,
N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-(4-fluorobenzyl)guanidine ,
N-[3-(thien-2-ylmethyl)pyrid-2-yl]-N'-benzylguanidine,
N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-4-cyanobenzylguanidine,
N-(3-(1-(4-methoxyphenyl)ethyl)pyrid-2-yl)-N'-benzylguanidine,
N-[3-benzylpyrid-2-yl]-N'-(2-chlorobenzyl)guanidine,
N-(3-benzylpyrid-2-yl)-N'-(4-chlorobenzyl)guanidine,

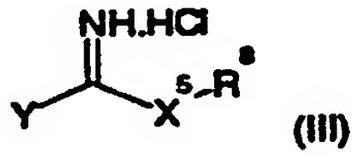
N-(3-benzylpyrid-2-yl)-N'-(4-methylbenzyl)guanidine,
N-[3-benzylpyrid-2-yl]-N'-(4-methoxybenzyl)guanidine,
N-(3-benzylpyrid-2-yl)-N'-benzyl-N"-hydroxyguanidine,
N-[3-benzylpyrid-2-yl]-N'-benzyl-N"-methoxyguanidine,
N-(3-benzylpyrid-2-yl)-N'-phenylguanidine,
N-[3-(thien-2-ylmethyl)pyrid-2-yl]-N'-phenylguanidine,
N-[3-(4-hydroxybenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-[3-(4-methoxybenzyl)pyrid-2-yl]-N'-phenylguanidine,
N-(3-benzylpyrid-2-yl)-N'-(4-chlorophenyl)guanidine,
N-3-(4-hydroxyphenyleth-2-yl)pyrid-2-yl-N'-phenylguanidine,
N-[3-(4-methoxyphenylethen-2-yl)pyrid-2-yl]-N'-phenylguanidine, or
N-[3-benzylpyrid-2-yl]-N'-phenyl-N"-dimethylguanidine;
or a pharmaceutically acceptable salt thereof.

8. A process for preparing a compound according to claim 1 which comprises:

(A) for compounds in which R^5 is hydrogen, X^4 is CH_2 and X^5 is a single bond or CH_2, reaction of a compound of structure (II):


(II)

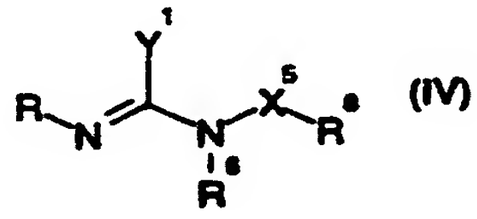
in which R and R^4 are as described for structure (I) with a compound of structure (III):


(III)

in which X^5 is a single bond or CH_2 and R^8 are as described for structure (I) and Y is a leaving group;

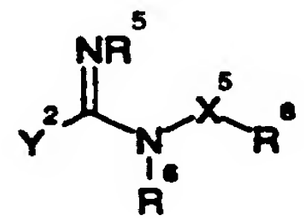
(B) for compounds in which X^4 is NR^6 and X^5 is a bond or NR^7, reaction of

(1) a compound of structure (IV)


(IV)

in which R, R^6, R^8 are as described for structure (I), X^5 is a bond or NR^7, and Y^1 is a leaving group with an amine of structure H_2NR^5 in which R^5 is as described for structure (I); or

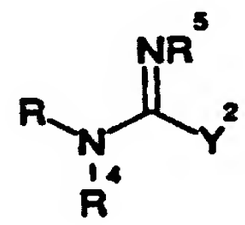
(2) reaction of a compound of structure (II) with a compound of structure (V)



(V)

in which Y^2 is a leaving group and R^5, R^6 and R^8 are as described for structure (I) and X^5 is a bond or NR^7; or

(3) reaction of a compound of structure (VI):



(VI)

in which R, R^4 and R^5 are as described for structure (I) and Y^2 is a leaving group, with a compound of structure (VII):

$$HNR^6X^5R^8 \quad (VII)$$

in which R^6 and R^8 are as described for structure (I) and X^5 is a bond or NR^7,

and optionally thereafter, forming a salt.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

10. A compound according to any one of claims 1 to 5 for use in therapy.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/01447

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D213/75 C07D239/42 C07D241/20 C07D401/12 C07D417/12
C07D409/06 A61K31/44 A61K31/50 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO,A,93 15055 (SMITHKLINE BEECHAM INTERCREDIT) 5 August 1993 see the whole document ---	1-10
A	EP,A,0 060 730 (IMPERIAL CHEMICAL INDUSTRIES PLC) 22 September 1982 see the whole document ---	1,3,9,10
A	EP,A,0 060 697 (IMPERIAL CHEMICAL INDUSTRIES PLC) 22 September 1982 see the whole document ---	1-10
A	EP,A,0 055 179 (MERCK & CO. INC.) 30 June 1982 see claims; example 1 -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 August 1994	18. 08. 94
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